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COST-EFFECTIVENESS ANALYSIS OF SIMULTANEOUS PANCREAS- KIDNEY TRANSPLANTATION

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This is to certify that I have examined this copy of a doctoral thesis by

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and have found that it is complete and satisfactory in all respects,
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TABLE OF CONTENTS

Title Page i

Acknowledgements ii

Table of Contents iii

List of Tables vii

List of Figures ix

Abstract x

Chapter 1 Introduction

I. Transplantation in Persons with Diabetes End-Stage Renal Disease and Third-Party Coverage 1

II. Clinical Benefits and Health-Related Quality of Life Outcomes of SPK 4

III. Prior Economic Analyses of SPK 5

IV. Statement of the Problems 7

V. Research Objectives 8

Chapter 2 Literature Review

I. Costs Associated with Diabetes and ESRD 10

II. Current Status of Simultaneous Pancreas-Kidney Transplantation 15

- A. Available transplant options for patients with ESRD and IDDM 15
- B. Risks due to pancreas transplantation 16
- C. Effects on glucose metabolism of pancreas transplant 19
- D. Effect on secondary diabetic complications of pancreas transplant 19
- E. Effect on quality of life of pancreas transplant 20
- F. Section summary 22

III. Guidelines for Cost-Effectiveness Analysis: The U.S. Panel 23

- A. Overview 23
- B. Theoretical framework of CEA in health care 25
- C. Estimation of resource consumption 28
- D. Valuing health consequences 31

E. Section summary 32
IV. Health-Related Quality of Life Based Utilities 33
A. Quality of Well Being Scale 35
B. Utilities indices derived from Medical Outcomes Study Short Form Health Survey 35
V. Cost-Effectiveness Analyses in Kidney and Pancreas Transplantation 37
A. CEA of kidney transplantation vs. dialysis 38
B. CEA of new immunosuppressive agents and preventive strategies for infectious complications in kidney transplant recipients 41
C. CEA of kidney and pancreas transplantation in patients with diabetic ESRD 43
D. Section summary 46
VI. Chapter Summary 47

Chapter 3 Theoretical model

I. Framework of Cost-Effectiveness Analysis 49
II. Health States Transition Model 52
III. Models for Transplant Choice and Utility Outcome 54
A. Selection bias on an estimation of treatment effect 54
B. Determinants of transplant choice 55
C. Factors affecting utility outcome 57
D. Justification of selectivity-corrected model 58

Chapter 4 Methodology

I. Data Sources 60
II. Markov Model 64
III. Computation of Transition Probabilities Death and Graft Failure Rates 66

IV. Estimation of Costs 68
- A. Algorithm handling Medicare claims data 69
- B. Components of costs for each health state 71
- C. Transplant surgery costs 72
- D. Follow-up costs 74
- E. Model for predicting costs 76

V. Estimation of HRQOL-based Utilities 77
- A. Utilities assigned to Markov model 77
- B. A longitudinal study of QOL (Gross et al.) 79
- C. Mathematical approach for selection bias problem 81
- D. Variables in the transplant choice model and utility estimation model 83

VI. Reference Case Analysis and Sensitivity Analyses 84

VII. Statistical Analyses 85

VIII. Limitations 86

Chapter 5 Results

I. Patients Characteristics 88
- A. SPK recipients enrolled in Medicare ESRD Program 88
- B. SPK recipients vs. KTA recipients in the study sample 90

II. Comparison of Patient and Kidney Graft Survivals between SPK and KTA 91

III. Transitional Probabilities Assigned to Health States in Markov Model 95

IV. Cost Estimates 100
- A. Costs of hospitalization for transplant surgery 101
- B. Annual total costs 102

V. Utility 106

A. Utilities for health states of KTA graft functioning and SPK both graft functioning 106

B. Utilities used in Markov model 113

VI. Cost-Effectiveness in the Reference Case 116

VII. Sensitivity Analysis 118

Chapter 6 Discussion and Conclusion

I. Summary of Major Findings 121

II. Discussion of Related Studies and Study Limitations 123

III. Implications to Health Care Financing Policy 130

References 133

Appendix 146

LIST OF TABLES

Table 2.1 Costs associated with diabetes complications 12
Table 2.2 Costs associated with kidney transplantation from HCFA ESRD Program 14
Table 2.3 Patient and graft survival rates (%) in diabetic ESRD patients by year after transplantation 17
Table 2.4 Age and health specific mean predicted QWB scores (SD) from SF-36 profiles 36
Table 4.1 Patient inclusion criteria and variables required 62
Table 4.2 Inclusion criteria for sample patients providing transplant surgery cost ratio 73
Table 4.3 Cost components (to be converted into 1998-constant dollars) and data sources 75
Table 4.4 Data sources for utilities 78
Table 4.5 Variables in selectivity-corrected models 84
Table 5.1 Demographic characteristics and selected outcomes of SPK recipients enrolled and not enrolled in Medicare ESRD Program 89
Table 5.2 Demographic characteristics of SPK and KTA recipients in the reference population (N=12,593) 91
Table 5.3 Adjusted patient survivals to 4 years after transplant for the reference population (N=12,593) 92
Table 5.4 Death rate ratio for patients receiving transplants during 1988-1993 and surviving for a minimum of 4 years after transplant (N=4,245) 93
Table 5.5 Adjusted patient survivals to 11 years after transplant for those who received transplant during 1988-1993 and survived through 4 years after transplant 93

Table 5.6 Failure rate ratio of kidney graft for patients receiving transplants during 1988-1993 whose kidney graft functioned for a minimum of 4 years after transplant (N=3,837) 94

Table 5.7 Adjusted kidney graft survivals to 11 years after transplant for those who received transplant during 1988-1993 and their graft survived through 4 years after transplant 95

Table 5.8 Probabilities of transition between health states for KTA 97

Table 5.9A Probabilities of transition between health states for SPK 98

Table 5.9B Probabilities of transition between health states for SPK 99

Table 5.10 Mean predicted cost and length of hospital stay for transplant surgery by transplant year 101

Table 5.11 Mean predicted annual costs by health state in each year following transplantation 103

Table 5.12 Mean predicted costs by health state of the reference population 104

Table 5.13 Sociodemographic and medical characteristics at baseline 107

Table 5.14 Parameter estimates from probit models: probability index for SPK (=1) vs. KTA (=0) 109

Table 5.15 Selectivity-corrected and ordinary least squares estimates for utility: whole sample 111

Table 5.16 Utilities for health states assigned to the reference case analysis 114

Table 5.17 Cost effectiveness for the reference case based on mean Characteristics of the reference population 117

Table 5.18 Results of sensitivity analyses 119

LIST OF FIGURES

Figure 3.1 Health state transitions for KTA 53

Figure 3.2 Health state transitions for SPK 53

Figure 3.3 Models for transplant choice and utility outcome 56

Chulaporn Limwattananon

324 words

ABSTRACT

Simultaneous pancreas-kidney transplant (SPK) is increasingly viewed as a treatment of choice for persons with type I diabetes and renal failure. However, the benefits of SPK *vs*. kidney transplant alone (KTA) with continued insulin therapy have not been thoroughly evaluated, particularly by using the most comprehensive available data sources or most powerful analytic techniques for estimating survival.

The primary objective of this study is to examine the incremental cost-effectiveness of SPK as compared to KTA, using a Markov model. Main outcomes include life expectancy, quality-adjusted life years (QALYs), and lifetime costs. Patient and graft survival rates came from the Medicare ESRD Program for kidney transplant and United Network for Organ Sharing for pancreas transplant (1988 to 1998). Cox proportions hazard models were used to estimate the transition probabilities. The Medicare payment databases (1991 to 1998) were used for enumeration of cost estimates. The annual cost estimates were adjusted for case-mix differences using generalized linear models based on gamma distribution with log-link function. Utility estimates were the predicted Quality of Well-Being scores from a longitudinal QOL study and values from published literature. The utilities from the QOL study were adjusted for selection bias using selectivity-corrected models.

The major findings are as follows. Estimated life expectancy is 13.4 years for an SPK recipient and 10.6 years for a KTA recipient. When the life expectancy is adjusted by quality of life, SPK generates 9.2 QALYs and KTA generates 6.4 QALYs. Lifetime costs of treatment are $407,336 for SPK and $319,633 for KTA (1998 U.S. dollars). The incremental cost-effectiveness ratios of $30,773 per year of life gained and $33,996 per additional QALY (discounted at 3%) for SPK represent a good monetary value for investment.

The results from this study provide explicit information based on the health care sector perspective about the incremental benefits and costs of choosing one transplant procedure over another for type I diabetic ESRD patients. SPK rather than KTA should be offered to this population.

CHAPTER 1

INTRODUCTION

This chapter discusses simultaneous pancreas-kidney transplant (SPK) and kidney transplant alone (KTA) in persons with type I diabetic end-stage renal disease, focusing primarily on economic aspects. Until recently Medicare did not cover the additional cost related to pancreas transplant surgery for SPK. In the absence of randomized clinical trials, the marginal clinical and health-related quality-of-life (HRQOL) benefits of pancreas transplants in conjunction with kidney transplants have been controversial. Cost-effectiveness analysis of the two procedures is warranted. A few early cost-effectiveness analyses have been conducted, and each has substantial limitations. This chapter contains the statement of the problem and a discussion of the research objectives.

I. Transplantation in Persons with Diabetic End-Stage Renal Disease and Third-Party Coverage

End-stage renal disease (ESRD) is a catastrophic illness with very high treatment costs. Diabetes is the leading cause of ESRD in the United States, accounting for 32.6% of all ESRD cases (USRDS, 1999a). For patients with ESRD and insulin-dependent diabetes (IDDM), KTA and SPK are both acceptable therapies according to the American Diabetes Association's recommendations (ADA, 1998). Until now, most patients with diabetic ESRD who seek transplants receive KTA with continued insulin therapy. Despite high transplant surgery costs on average, the costs of immunosuppressive therapy for maintaining grafts in KTA recipients are much less than in those receiving continued renal dialysis (Eggers, 1992). Importantly, Medicare will pay for the kidney transplant surgery cost and follow-up costs for up to 3 years after successful kidney transplantation, regardless of the recipient's age. SPK appears to be a preferable alternative for patients with IDDM who are in need of a kidney transplant and, consequently, are obligated to use immuno-suppressive drugs. The reason one would prefer the additional pancreas transplant is that SPK is presumed to prevent or delay secondary diabetes complications and to improve the patient's quality of life (QOL) (Gross et al., 1998). Patients no longer are obligated to use insulin therapy, and insulin-related diet or lifestyle restrictions. Among the major clinical disadvantages, SPK is considered a major surgery and re-admission rates among SPK recipients during the first year after transplantation are relatively high (Holohan, 1995). The major financial disadvantage is that most candidates for SPK are Medicare ESRD beneficiaries, and in the past, Medicare did not pay for the surgery charges specific to pancreas transplant of a SPK procedure. Some candidates for SPK have difficulty finding a third party to pay for the additional pancreas transplant.

Medicare began to finance treatments for ESRD in July 1973. Since then, Medicare has become the major third-party payer for persons with ESRD. In 1996, the total ESRD costs in U.S. were estimated to be $14.55 billion and Medicare payments accounted for $10.96 billion (USRDS, 1999b). Medicare as the primary payer reimbursed $290.3 million for 12,720 persons with diabetes who had received kidney transplant and $671.1 million for 44,147 non-diabetic persons who had received kidney transplant in 1996 (USRDS, 1999c). The difference in average payments per person of $22,822 versus $15,202 between the above two groups of kidney transplant recipients represents additional costs associated with diabetes treatment and its complications.

For persons with IDDM, pancreas transplant is the only treatment that can establish an insulin-independent state with euglycemia and normal glycosolated hemoglobin (Sutherland, 1997). Pancreas transplant alone is not a common procedure, however, since many clinicians feel continued insulin use is less burdensome and less risky than transplant surgery and lifelong immune suppression. Adding a pancreas graft to a kidney transplant for SPK surgery is more widely accepted. Currently, SPK increasingly is performed in patients with severe secondary complications of diabetes including kidney failure. As of December 1998, approximately 7,500 patients in the U.S. received SPK (IPTR, 1999). The overall technical failure rate fell from 16% in 1987-89 to 9% in 1994-96 (Sutherland, 1997). As of September 1999, there were fewer than 2,000 candidates for SPK on the U.S. national transplant waiting list, whereas about 9,000 persons with diabetes and ESRD were listed as waiting for cadaveric KTA (UNOS, 2000).

Even though the current success rate of SPK is comparable with other solid organ transplants, the financing mechanism for SPK varies substantially across third-party payers. Not until July 1, 1999 did Medicare start to cover a pancreas transplant for Medicare beneficiaries when it is performed simultaneously with or after a Medicare covered kidney transplant. However, this policy has no special provisions related to the beneficiaries who are managed care participants. Managed care plans are required to provide all Medicare covered services. This point is crucial for people who become Medicare recipients as a result of a kidney transplant that is paid for by a third-party carrier. SPK performed on patients with diabetic kidney failure is a reimbursable procedure for most of the major private insurance companies. However, the reimbursement process generally is subject to a prior authorization requirement (Insulin Free Organization, 2000). The additional pancreas transplant coverage typically is approved on an individual basis. The proportion of health maintenance organizations that paid for pancreas transplantation in addition to kidney transplantation has increased from 43% in 1986 to 55% in 1992 (Evans, 1994). Until now, the reimbursement policy of SPK among third-party payers has yet been consistent.

II. Clinical Benefits and Health-Related Quality of Life Outcomes of SPK

In terms of current patient survival and graft survival rates, SPK compares favorably to KTA in population with diabetes (Sutherland, 1997). Except for its known beneficial impact on nephropathy (Fioretto, et al., 1998), the issue of pancreas transplant's impact on secondary diabetic complications is still controversial (Holohan, 1995; Barnette, 1997). Diabetic patients with ESRD are likely to have concomitant diabetes complications like vasculopathy and retinopathy. The higher survival rate in SPK recipients probably reflects both selection of healthier patients for the combined procedure and potentially additional benefits from adding a pancreas transplant (Sutherland, 1997). Selection criteria for candidates of SPK have not been delineated in most publications (Holohan, 1995). Most transplant centers report that the patient's preference is among the major determinants of choice of SPK versus KTA. This self-selection bias can confound assessment of clinical benefits. The additional benefits of SPK relative to KTA need to be evaluated after the impact of the transplant choices on outcomes are controlled experimentally or through statistical adjustment.

The major claimed benefit of SPK over KTA is an improvement in QOL-related outcomes. Despite a lack of hard evidence, most practitioners accept that SPK can improve the HRQOL of the recipients (Pirsch et al., 1996). Most studies had a limited follow-up period, the long-term benefits have not been thoroughly evaluated yet. Researchers have found few areas where either QOL or HRQOL outcomes of SPK recipients significantly exceeds or is distinguishable from those outcomes with KTA. However, a consistent finding shows that SPK improves patient perceptions about disease-specific issues such as satisfaction with diet flexibility and health management while KTA does not (Gross et al., 1998). Due to the present ambiguity, with respect to clinical and HRQOL benefits of SPK versus KTA, a systematic evaluation of patient and societal values for these two competing medical interventions is needed.

SPK and KTA seem to be close competitors when considering their short-term effects, however, their long-term effects have not been well-studied. SPK appears to generate a higher initial cost and similar QOL to KTA in the short term, but it probably contributes a better QOL over time that will outweigh the initial cost differential in the long term. Thus far, no well-designed studies on QOL outcomes of SPK have adjusted for the self-selection bias or have included long-term follow-up.

III. Prior Economic Analyses of SPK

Four formal analyses of cost and cost-effectiveness of SPK have been reported. None of these prior studies adhered to the current CEA guidelines by the U.S. Panel on Cost-Effectiveness in Health and Medicine (Gold et al., 1996). For example, these studies did not discount cost and health outcomes to the present value.

In one study, the analysis covered only the transplant surgery cost of SPK that was performed in the late 1980s (Evans et al., 1993b). The second, a cost-effectiveness analysis conducted by the Office of Health Technology Assessment summarized transplant surgery costs and one-year follow-up costs during 1990-1993 for SPK and KTA (Holohan, 1995). This study had a post-transplant time horizon limited to three years which was less than the expected survival period. The analysis did not consider all possible heath states of the transplant recipients by assuming that kidney graft failure and deaths occurred in similar rates in both groups. Assigned utility weights were hypothetical. The study concluded that SPK would be more cost-effective than KTA if the annual cost of treating hyper/hypoglycemia in KTA recipients was greater than $15,000.

Douzdjian et al. (1998 and 1999) reported SPK was a cost-effective therapy for a patient with IDDM and ESRD. Using a 5-year decision tree model, the expected cost effectiveness ratio was $27,070 per quality adjusted life year (QALY) gained when comparing SPK and cadaveric KTA. In their second report, comparing SPK and living donor kidney transplantation followed by pancreas transplant, the difference was $13,535 per QALY gained. The utility for SPK recipients with both grafts functioning was assigned the value of 1, and that for KTA with continued insulin therapy was 0.6, obtained by using standard gamble technique. In general, these transplant recipients all suffered from diabetic retinopathy and neuropathy on top of uremia neuropathy before transplantation, thus, the obtained value of 1 for the SPK recipients with both grafts functioning is too high. It is unlikely that these patients would have the perfect health given aging and cumulative effects of IDDM and ESRD.

IV. Statement of the Problems

Major advances in SPK procedures have been made over the past decade as evidenced by increases in one- and three-year patient survivals and a decrease in pancreas graft failure rate. However, there have not been adequate studies of long-term benefits of pancreas transplant in SPK for persons with type I diabetic ESRD. Third-party payment for SPK also varies substantially compared to the payment for KTA. Expensive medical technology like SPK and KTA would consume a significant proportion of any health care budget. Whether payment for the additional pancreas transplant is economically sound is a critical issue in our cost-conscious society. A cost-effectiveness analysis (CEA) of SPK and KTA could help in making appropriate decisions on financing these two competing procedures for type I diabetic ESRD patients.

To make a valid comparison on cost and effectiveness between these two competing procedures, a randomized controlled trial of SPK and KTA is needed. The results of such a trial, even if it were begun today, would not be known for many years. In contrast, with currently available national data and analytic methodology, we can conduct a CEA within a year and make the most of the information we have to date to assess the two transplant options. This CEA could provide guidance until such time as the results of a randomized trial are available. Nationally longitudinal transplant registry databases and Medicare claims data are available and can provide information on long-term benefits and costs, but this investigation has not been done. A CEA of SPK based on a model of lifetime benefits and costs using estimates from such data sources is warranted.

For ESRD patients, KTA is considered the usual standard of care because KTA is well-accepted as a cost-effective treatment over dialysis (Evans, 1999). The fact that kidney transplants represent a better investment of heath care resources compared with dialysis is established. KTA is a close comparator of SPK for ESRD patients with type I diabetes. Medicare currently covers both KTA and SPK. If the incremental cost-effectiveness ratio of SPK versus KTA is not beyond a financially acceptable level, one might conclude that SPK should be performed in all patients who are cadaveric KTA candidates with type I diabetes and have no contra-indications, unless dictated by the availability of organ. Otherwise, all available cadaveric pancreas organs will not be used efficiently. It is timely to assess the cost-effectiveness of SPK which has only recently advanced to having patient and graft survival rates comparable to KTA. Modeling based on the most recent data is justified when primary data from randomized trials are not available.

V. Research Objectives

The main research question is how much more we would have to pay for an additional year of life gained from an SPK option for type I diabetic ESRD patients. The primary objective of this study is to determine the cost-effectiveness ratio of SPK as compared to cadaveric KTA with continued insulin therapy. A cost-effectiveness ratio is calculated over the expected lifetime of the transplant recipients as dollars per QALY gained. According to the primary objective, this study aims to answer two questions. The first question is, "if SPK was performed in all kidney transplant candidates who had type I diabetes as a cause of renal failure and availability of cadaveric organ donors was not problematic, what would be the lifetime benefits and lifetime costs of SPK?" The second question is "would more costly SPK be preferable to KTA with continued insulin therapy from the perspective of the health care sector?" This CEA follows the recently developed guidelines proposed by the U.S. Panel on Cost-Effectiveness in Health and Medicine (Gold et al., 1996).

To fulfill the primary objective, this study determines (1) life expectancy, (2) expected lifetime costs, and (3) expected quality-adjusted life years (QALY) for both SPK recipients and KTA recipients with continued insulin therapy. In addition, the following research questions are addressed.

1. Whether or not the post-transplant costs of SPK recipients with successful graft function change over time.
2. Whether or not the post-transplant costs of KTA recipients with successful graft function change over time.
3. For those with successful graft function, are the short-term utilities, measured at year one post-transplant, in SPK recipients higher than those in KTA recipients?
4. For those with successful graft function, are the long-term utilities, measured at year three post-transplant, in SPK recipients higher than those in KTA recipients?

These research questions have not been evaluated and the results are important for policy makers, patients/families and health care providers.

CHAPTER 2

LITERATURE REVIEW

This chapter is divided into five main sections. The first section describes costs associated with type I diabetes and end-stage renal disease. The second chapter presents data on risks and benefits of simultaneous pancreas-kidney transplant. The third section summarizes guidelines on CEA and the theories behind them, which facilitate comparability across studies. These recommendations were followed in developing the framework and the analysis plan for the present study. In the fourth section, utilities derived from health-state classification systems that have become common techniques used in CEA are covered. The fifth section is a review of the framework and methodological approaches of previous CEAs of kidney and pancreas transplants.

I. Costs Associated with Diabetes and ESRD

Type I diabetes affects approximately 500,000 individuals in the U.S. (CDC, 1999). Its long-term complications include retinopathy, nephropathy, neuropathy, and cardiovascular disease. However, end stage renal disease is one of the most serious complications. In 1995, 27,851 people with diabetes developed ESRD, and 98,872 people with diabetes underwent dialysis or kidney transplant (CDC, 1999). Although only about 5-10% of people with diabetes are insulin-dependent, type I diabetes accounts for almost 30% of the total costs attributable to diabetes (Songer, 1992).

Given the number of published articles on diabetes and its complications, it could be assumed that several good sources of cost data on a per-patient basis for economic analyses would be available. In fact, very few studies provided comprehensive cost estimates. Two reports, the Diabetes Complications and Control Trial (DCCT) (1995) and a study by O'Brien et al. (1998) were particularly well-done and their findings are described below.

The DCCT trial (1995) compared efficacy of intensive and conventional insulin therapy for type I diabetes. The conventional insulin therapy in the control group, however, was actually more intensive than usual care in the community. The cost analysis for this trial also enumerated costs by using micro-costing techniques. A clinic cost questionnaire was used to gather data on details of the time and resources required for the provision of the care. Costs were calculated as the product of the resources used and the unit costs of those resources. Unit costs for labor and fringe benefits were derived from the DCCT's budget. Unit costs for equipment and supplies were derived from manufacturers' average wholesale prices, which were amortized over the expected lifetime for the equipment. Unit costs for tests, procedures, and consultation and also costs for ambulatory services, emergency room, and hospital services were derived from Medicare. The estimates of cost for initiation of intensive therapy were $2,824 for multiple daily injections (MDI), and $2,903 for continuous subcutaneous insulin infusion (CSII). The costs of crossing over from MDI to CSII were $476 for inpatient initiation therapy and intensive follow-up, and only $41 for the reverse using management calls.

The annual costs were $4,014 for MDI therapy, $5,784 for CSII, and $1,666 for conventional therapy. These annual costs take into account the occurrence of side effects and their treatment. In addition, IDDM patients normally need several routine checks-ups for complications with annual costs of $948 for photocoagulation, $80 for renal evaluation, $124 for neurologic evaluation, and $725 for angiotensin-converting enzyme inhibitors. These costs are presented in 1994 U.S. dollars.

Table 2.1 Costs associated with diabetes complications

Complication	Cost (in 1996 U.S. dollars)			
	Discharges	Acute Hospital Cost	Event Cost	Annualized State Cost
Cardiovascular				
Acute myocardial infarction	26,974	16,520	27,630	2,185
Angina	3,922	5,087	2,477	1,082
Cerebrovascular				
Ischemic stroke	23,665	9,236	40,616	9,255
Transient ischemic attack	5,289	5,261	6,204	45
Nephropathy				
Microalbuminuria	N/A	N/A	62	14
Gross proteinuria	N/A	N/A	69	23
ESRD	N/A	N/A	N/A	53,659
Retinopathy				
Background retinopathy	N/A	N/A	N/A	57
Macular edema	N/A	N/A	1,100	57
Proliferative diabetic Retinopathy	N/A	N/A	1.044	57
Blindness	N/A	N/A	N/A	3,468
Neuropathy				
Symptomatic neuropathy	N/A	N/A	218	N/A
First leg amputation	8,497	18,613	26,894	1,739
Second leg amputation	8,317	19,071	27,132	N/A

Source: O'Brien et al (1998)

Information on direct medical care costs in managing complications for type I diabetes is not available. Most economic studies of type I diabetes assumed such costs were similar to those in type II diabetes (Holohan, 1995; Wu et al., 1998). O'Brien et al (1998) conducted a study to estimate direct medical costs of diabetic complications on a per-patient basis for type 2 diabetes (Table 2.1). Acute care hospital costs were based on five state discharge databases in 1994 and 1995, and a well-constructed algorithm was used to identify specific populations for each complication from the pool of diabetic discharges. Medicare fee schedules were used for laboratory services, physician procedure and visit fees. The costs of skilled nursing facilities and home health care were taken from Medicare data. For each complication, the event costs were those associated with resource uses that were specific to the acute episode and any subsequent care occurring in the first year. The state costs were the annual costs of continued management.

The Medicare ESRD Program covers 92% of dialysis patients and 93% of kidney transplant recipients in the U.S. (Sullivan et al., 1997). Medicare, therefore, is considered a good data source for these populations. The following annual cost data are for those 20 to 64 years old who had Medicare as their primary payer in 1996 (USRDS, 1999c). The total costs were estimated directly from the Medicare payments taking into account 20% copayment amounts on Part B services and the Part A deductible. For any treatment modalities for dialysis, average annual costs per person were $38,447 for persons with diabetes, and $28,589 for persons without diabetes. For persons who received a kidney transplant, average annual costs per person were $22,822 for persons with diabetes and $15,202 for persons without diabetes. The large differences in the average costs per person per year represent additional costs associated with diabetes therapy and management of diabetic complications. In general, costs, incurred in the first year of events, are substantially higher than those of the other years. The average costs per person per year reported here are based on the mixture of the incident cases and prevalent cases.

Table 2.2 Costs associated with kidney transplantation from HCFA ESRD Program (1995 U.S. dollars)

Monthly cost of dialysis	$4,280
Transplant organ procurement and procedure	
First	$64,660
Repeat	$70,480
Transplant follow-up care/immunosuppressive therapy (year 1)	$43,570
One-time cost of graft-failure	$29,200
Monthly cost of functioning graft after month 12	$1,160

Source: Horberger et al., 1997

Table 2.2 presents costs associated with the first year of kidney transplantation and maintenance costs after receiving kidney transplantation under the Medicare Program. They were used in a recent CEA involving kidney retransplant policy (Horberger et al., 1997). The reports from the Medicare ESRD Program or USRDS do not provide separate analyses for those who underwent KTA, SPK or pancreas after kidney transplantation (PAK). In addition, costs associated with kidney graft functioning and graft failure across years post-transplant or after an incident of graft failure are not available. As kidney transplant recipients who had diabetes may have secondary diabetes complications that may worsen over time and generate a substantial cost on top of maintaining kidney graft, such cost estimates over time are essential for economic analyses. On the basis of Medicare databases on kidney transplantation in ESRD Program and claim data, the investigation of the costs over time specific to the KTA recipients with type I diabetes is possible.

In summary, with the chronic nature of type I diabetes and the potential for development of multiple costly complications, costs relating to type I diabetes should be a major concern in health care financing. It is evident that costs relating to ESRD diabetes are substantial. At the present time, there are emerging therapies designed to offer an alternative to conventional insulin therapy such as intensive insulin therapy, pancreas transplantation, or islet cell transplantation which may improve glycemic control and help reduce the incidence of some complications. An important question involves which treatment strategy is preferred when taking into account costs and health outcomes from the perspective of health care sectors or society. To answer this question, an economic evaluation such as a CEA is warranted. The present study evaluates cost-effectiveness of SPK in patients with diabetic ESRD compared to KTA.

The next section provides the reviews of current risks and benefits associated with SPK. Several advancements have been made on surgical techniques and immunosuppressive therapy of SPK in 1990s.

II. Current Status of Simultaneous Pancreas-Kidney Transplantation

A. Available transplant options for patients with ESRD and IDDM

The only treatments for IDDM that can establish insulin independence include either pancreas transplant or dispersed islet cell transplant (Sutherland, 1997). To date, pancreas transplant has been more successful than islet cell transplant, and has also recently become a popular alternative treatment modality for patients with IDDM due to great improvements in the surgical techniques and an advancement in immunosuppressive therapy.

Because of the obligation to immunosuppressive treatment, an additional pancreas transplant to kidney transplant for IDDM patients who have progressive uremia nephropathy is considered acceptable by most clinicians. The most common pancreas transplant procedure is performed simultaneously with a kidney transplant from a single cadaver. The other option is a subsequent cadaveric pancreas transplant after receiving a living donor for kidney transplant (i.e., PAK). One benefit of SPK is that an increase in serum creatinine as a marker for rejection of the kidney frequently occurs prior to a decrease in pancreas allograft function, so that it can be an early signal for a rejection episode of the pancreas. The technique in performing segmental pancreas transplant from a living donor has not been very successful, so few patients choose this procedure.

Although islet transplant does not require a major operation surgery, the islet preparation technique is very complicated. In addition, isolated islets are sometimes more prone to rejection than an intact organ. Approximately 200 islet transplant procedures have been performed in the 1990s, and less than 10% of the recipients have achieved insulin-independence at 1 year (Sutherland, 1997).

B. Risks due to pancreas transplantation

Historically high surgical complication rates of pancreas transplant have been declining (Troppman et al., 1998). A 12-year retrospective review was conducted on pancreas transplants performed at the University of Minnesota. The study compared the incidence of early surgical complications in type 1 diabetes patients who underwent pancreas transplantation between June 1,1985, and April 30, 1994 (N=367), with the incidence in patients who underwent the procedure between May 1, 1994 and June 30, 1997 (N=213). 32.4% of the recipients in the first period required early relaparotomy compared with only 18.8% in the second period, which was a significant difference. The death rate in recipients requiring early relaparotomy also decreased significantly from 9% to 4%. Vascular graft thrombosis also dropped from 12.1% to 5.8%. In addition, the incidence of intra-abdominal infections significantly dropped from 18% to 5.8%. The differences in vascular thrombosis may be related to a change in thrombosis prophylaxis with the use of low-dose heparin and aspirin postoperatively. Prophylaxis with fluconazole antifungal therapy, begun in 1994, may have played a role in lowering the rate of postoperative intra-abdominal infections.

Table 2.3 Patient and graft survival rates (%) in diabetic ESRD patients by year after transplantation

	Year 1	Year 2	Year 3	Year 4	Year 5
SPK[1]					
Patient survival[2]	94	92	90	85	80
Graft survival					
- Kidney*	90	87	84	75	72
- Pancreas	83	81	80	70	65
Cadaveric kidney transplant[1,3]					
Patient survival[2]	92	88	NA	NA	72
Graft survival					
- Kidney	88	79	72	NA	59

[1] Unadjusted rates for the most recently available years

[2] Not classified by conditions of graft functional status

[3] The data include all kidney transplant regardless the additional pancreas transplant status.

Sources: International Pancreas Transplant Registry (IPTR), 1998 and 1999
United States Renal Data System (USRDS), 1999

The introduction of new immunosuppressive drugs, such as tacrolimus and mycophenolate mofetil (MMF), is associated with an improvement in pancreas graft survival rates and a lower rate of rejection; improvements are expected to continue (IPTR, 1999; Jordan et al., 1999). Complete steroid withdrawal was possible in 65% of recipients with functioning pancrease taking FK506 as a primary agent for maintenance therapy (Jordan et al., 1999). The current 1-year graft survival rates for U.S. patients are 83% for the pancreas and 90% for the kidney (IPTR, 1999). These rates compare favorably to the 88% 1-year graft survival rate for KTA in a person with type I diabetes as shown in Table 2.3.

Young SPK recipients (less than 45 years old) without cardiac risk factors showed better results in terms of technical failure rate, graft functional rate, and patient survival rate (Gruessner et al., 1994). The technical failure rate was about twice as much in those who were at least 45 years old. SPK and PAK recipients who were at least 45 years old had three times the risk of dying as those who were younger. In addition, the risk of dying for patients with cardiac disease was about 4 times higher than those without cardiac disease. Gruessner et al. (1994) concluded that patients with diabetic ESRD who are older than 45 years should select KTA or combined islet/kidney transplantation, unless the patients accept the additional risk of pancreas transplantation as a trade off for a potentially better quality of life.

For SPK, there exist problems associated with a longer hospital stay for transplant surgery, an increase in rate of hospital readmission and the higher costs, as compared to cadaveric KTA, within the first year of transplant. Bladder drainage as a procedure to achieve exocrine secretions for pancreas transplant is commonly performed because it allows monitoring of the amylase enzyme in urine which can detect an acute rejection of the pancreas graft before the overt hyperglycemia. However, bladder drainage produces several urological and metabolic complications, and many SPK recipients eventually need to have a conversion to enteric drainage. In one study, 90% of patients in the SPK group were hospitalized during the first year of follow-up, whereas only 68% of patients in the KTA did so (Gross et al., in press). At three years post transplant, the rates were 55% and 41% for the SPK and KTA.

C. Effect on glucose metabolism of pancreas transplant

A successful pancreas transplant can normalize glycemic control. (Fernandez et al., 1998; Tyden et al., 1998). Long-term followup studies showed that 60% to 92% of SPK recipients sustained a normal range of glycosylated hemoglobin levels for at least 5 years after transplant (Tibell et, 1990; Morel et al., 1991a). Reversible pancreatic rejection episodes do not adversely affect long-term glycemic control (Morel et al., 1991b). However, in SPK recipients with systemic venous drainage of the pancreatic allograft, hyperinsulinemia can be found. Hypothetically, hyperinsulinemia can cause the promotion of atherogenesis, but thus far there is no evidence that this hyperinsulinemia condition leads to cardiovascular morbidity after SPK (Hricik, 1998).

D. Effect on secondary diabetic complications of pancreas transplant

There is evidence that pancreas transplant can reverse neuropathy, prevent nephropathy, and stabilize retinopathy. Pancreas transplant recipients showed an improvement in autonomic neuropathy, as evidenced by improvement in Valsalva ratio and in gastric emptying (Kennedy et al., 1990; Hathaway et al., 1994). Histological signs of nephropathy were seen as early as two years after transplant in diabetic KTA recipients (Mauer et al., 1989). In PAK cases, reversal of lesions of diabetic nephropathy was found (Foretto et al., 1998). Ramsey et al. (1988) studied the impact of pancreas transplant on retinopathy. They compared the eyes of 22 pancreas transplant recipients to those of 16 patients with failed pancreas graft. No benefit was observed at 24 months, but there was a trend toward improvement at 36 months in the successful pancreas transplant group which did not reach statistical significance. However, a longer follow-up may be required to detect such benefits, as intensive insulin therapy resulting in tight glucose control was shown to prevent the onset and progression of retinopathy with the average follow-up of 6.5 years in DCCT study (1993). Hypothetically, it is possible that insulin independence achieved by pancreas transplant would have an effect on diabetic retinopathy in the long run.

SPK recipients had fewer self-reported diabetic complications than KTA recipients did at three years after transplant (Gross et al., in press). The benefits included halting and preventing further kidney disease, halting and improving nerve status, halting eye and cardiovascular disease, and less chance of amputation.

E. Effect on quality of life of pancreas transplant

A comprehensive review of QOL studies in pancreas transplant was published by Holohan (1995), and Gross et al. (1998). A consistent finding across studies is that pancreas transplant improves patient perceptions about diabetes-specific issues such as satisfaction with diet flexibility and health management. The major pitfalls of studies included small sample sizes, short follow-up periods, or no pre-transplant assessment. Several reports compared QOL outcomes of combined pancreas-kidney recipients (either SPK or PAK) with functioning pancreas and kidney grafts against those with nonfunctioning pancreas graft in order to evaluate the additional QOL benefits of pancreas transplant. These studies would have some negative effects from pancreas graft loss. Patients with graft loss (either pancreas or kidney) recalled their QOL prior to transplant significantly more positively than did patients with functioning grafts, despite an absence of corroborating evidence of pre-transplant differences (Adang et al., 1997).

Gross et al. (in press) conducted a prospective longitudinal study of patients with IDDM and renal dysfunction who received either SPK or KTA, with assessments at pre-transplant and one and three years post-transplant. The study patients were recruited from a single large transplant center and were not randomly assigned to the transplant. To reduce the problem due to healthier patients choosing SPK, the analysis was adjusted for baseline values of the dependent variables. The study questionnaire included generic measures of global QOL and SF-36 health survey, and HRQOL measures specific to diabetes. At one year after transplant surgery both SPK and KTA recipients reported better physical and mental health function, improved well-being, and greater life satisfaction. SPK patients, however, reported greater improvements than KTA patients in areas that are diabetes-specific, including satisfaction with health and treatment. At three years after transplant SPK recipients also reported less bodily pain, better physical functioning and perceived greater benefits to secondary complications to eyes, nerves, vascular system and kidney than KTA recipients. Their general health perceptions also were better. On the other hand, KTA recipients appeared to derive more positive mental health outcomes, and reported fewer emotional problems with role activities by three years after transplant. By year three, the median score among the SPK cohort was at the 30th and 51st percentiles of the general adult U.S. population in self-reported physical and mental health; the KTA cohort was at the 10th and 73rd percentiles. While the improved physical outcomes of SPK patients are consistent with perceived benefits to secondary complications, the mental health differences cannot be explained by the study data and warrant further study.

F. Section summary

To date, SPK has shown to offer successful clinical outcomes in terms of patient and graft survivals, fewer self-reported diabetic complications, and improved physical function and diabetes specific QOL. As SPK is an expensive surgery that has recently gained popularity, an analytical study like a CEA, that accounts for its costs and quality adjusted life year, is needed for supporting the more widespread application of this procedure. The next section summarizes how to conduct CEA using standardized methodology that will facilitate comparing the results across studies on various health interventions.

III. Guidelines for Cost-Effectiveness Analysis: The U.S. Panel

A. Overview

Cost effectiveness analysis is an analytical tool used to evaluate outcomes and costs of interventions designed to create better health and/ or longer life. The result of such evaluation typically is represented by a cost-effectiveness ratio (C/E ratio), if one alternative is not dominant by generating better health outcomes with a lower cost. The denominator reflects the gain in health from the treatment of interest, whereas the numerator reflects the cost of obtaining the health gained. Generally, outcomes of interventions are measured in different units, which limits broader applicability for comparing of the relative C/E ratios of various health interventions. A quality-adjusted life year (QALY) that incorporates survival and quality of life has been developed for the methodology of cost effectiveness studies. To inform policy makers for resource allocation, the relative values of cost in monetary unit per QALY gained can serve as a guide to which health interventions yield higher benefits. CEA using QALYs to evaluate outcomes is sometimes termed 'cost utility analysis'.

There has been a lack of common methodology in CEA during the past three decades which has limited its applicability to the health policy. In 1996, the Panel on Cost-Effectiveness in Health and Medicine announced a set of recommendations to standardize methodology. The Panel encouraged conducting a reference case or base case analysis for cost-effectiveness studies to facilitate the comparability across studies for policy decision making on health care resource allocation (Gold et al., 1996). With

uniformity in methodology, differences in C/E ratios should reflect true differences in costs per QALY gained among health care interventions rather than methodological differences.

The Panel recommended that a reference case analysis be based on a societal perspective reflecting public interest. The analysis should compare a health intervention of interest to a best-available alternative, a low-cost alternative, or a 'do-nothing' alternative, whichever is the most relevant to the real world practice. The boundaries of the analysis should be defined broadly enough to encompass the range of groups of people affected by the intervention and all types of costs and health consequences. The time horizon should be long enough to capture all relevant future effects of health care interventions. Items of resource uses to be included and how to appropriately measure and value them in the numerator and how to incorporate health consequences in the denominator were proposed. Costs and health effects should be discounted to present value at a rate consistent with the real economic growth and the real consumption rate of interest. Currently the Panel recommends 3% as the most appropriate real discount rate for a CEA, accompanied by a sensitivity analysis with a range of rates from 0% to 7%. However, to retain comparability with existing analyses, both 3% and 5% discount rates should be used in analyses for at least the next ten years.

A CEA based on the standard methodology should inform rather than dictate allocation of limited resources. Other considerations, such as access to services, helping the most vulnerable, equity, personal freedom, political feasibility, and etc. that cannot be quantified in the CEA need to be addressed in the real world decision. Certain options in decision making will be cost-effective from the societal perspective but may not be from the patient's perspective. Many healthcare providers find the societal perspective irrelevant for their own purposes. From the societal perspective, actual wholesale price or discounted wholesale price is proposed as one of the solutions in choosing unit costs of drug therapy. From the patient perspective these prices are lower than the amount of money they themselves need to pay. Some researchers are reluctant to accept the Panel recommendations when their objectives for conducting CEA are not relevant to providing the relative C/E ratio for prioritization of a variety of health care interventions.

B. Theoretical framework of CEA in health care

Welfare economic theories suggest that, for any given level of resources, society wants to maximize total aggregate benefits contributed from individuals (Arrow, 1963). The CEA in healthcare is based on the premise that health benefit is the ultimate outcome that societal decision-makers wish to maximize, subject to the availability of health care resources. It is assumed that each individual would maximize their expected happiness following certain conditions of rationality and logical consistency. This "utility function" reflects an individual's well-being, which is derived from consumption of goods and services. Overall welfare of the society is a function of individuals' utilities. Therefore, the summation of individuals' QALYs can be used to reflect total health benefits or effectiveness of health care interventions.

Arrow (1963) proposed that consumption of health and health care involve uncertainty about the risk of diseases and the effect of health care interventions. In the CEA of healthcare, measurement of effectiveness must reflect this uncertainty. Expected utility theory, hence, can be applied to CEA in the modeling of the preferences associated with health care interventions. According to the theory, each alternative action can be characterized by a set of possible outcomes and each outcome is associated with a probability and degree of utility. To choose the best action, the product of the outcome probability and the associated utility are summed across all outcomes related to each action. The expected utility reflects both ordinal rankings of the intervention's outcomes and strength of the outcome preference under uncertainty. QALY as a measure of effectiveness can be used to represent the expected utility if the individuals are willing to trade off years of life conditional on a given health state for fewer years at an ideal health state. Therefore, the standard gamble technique that is based on the expected utility theory often is considered the gold standard method of eliciting an individual's preference in CEA studies.

An estimation of the total cost of health care resources should be based on the value of the resources in their next best alternative use. In the absence of market imperfection, the price of a unit of output equals the resource cost of the last unit produced, and likewise the resource cost of the marginal unit produced equals the value of its inputs elsewhere. Hence, the market prices would reflect the opportunity cost of the resources used.

A controversial issue in CEA is the estimation of indirect costs that refer to productivity losses related to illness or death. These indirect costs were termed ‘productivity costs’ by the Panel. Because time also is a scarce resource that can be spent for other valuable purposes, these costs should be taken into account in CEA. The Panel has suggested not to impute the indirect costs associated with illness or death in the numerator, but a HRQOL measure should be used in the denominator to capture the effects of morbidity on productive time and leisure activities. This recommendation is made for consistency across reference case analyses.

Another controversial methodological issue relates to discounting of health outcomes. The social welfare foundation of CEA suggests that the QALY is an approximation of utility with nonzero time discounting. The real (inflation-adjusted) discount rate should be based on time preference or the difference in value people assign to events occurring in the present *vs.* the future. The Panel recommended that both costs and health outcomes occurring during different time periods should be discounted to their present values at the same rate. The Panel has recommended the investment rate of 3% be used at the discount rate. The rationale for discounting health outcomes is not to demean the value of future life. Rather, because lives and other utilities are being valued relative to dollars and because dollars are discounted to their present value, health benefits might be discounted at the same rate. This is not just for consistency across studies, but also to avoid Keeler paradox.

C. Estimation of resource consumption

Cost components

The perspective of the study is the major determinant of which resource uses are to be included in the analysis and how to identify and measure them. Luce and Brown (1995) meticulously provided a summary of the resources that should be included regarding the perspective chosen for an analysis. In the reference case analysis, the major costs incorporated in the numerator should include costs of health care services (direct health care costs), costs of patient time spent for the intervention (patient time cost), costs associated with care giving and costs associated with non-health impacts of the intervention (direct non-healthcare cost). Whether health care costs associated with unrelated illnesses in added years of life are included depends on its relevant to the treatment of interest.

Terminology and definitions

The Panel provides terminology and definitions involving resource consumption, allowing consistency of communication among researchers in this area. Direct health care costs include the costs of tests, drugs, supplies, equipment, medical facilities, and healthcare professional fees. Direct non-healthcare costs usually refer to costs of transportation, time family members or volunteers spend to provide care, etc. Patient time cost refers to the time a patient spends seeking care, participating in or undergoing an intervention.

Productivity costs are defined as the costs associated with lost or impaired ability to work or to engage in leisure activities due to sickness (morbidity cost), such as time for recuperation and convalescence and economic loss due to death (mortality cost). The Panel used the term 'productivity costs' instead of indirect costs and recommended that their intrinsic value should be captured by the utility outcome measure in the denominator. In the other words, we include only the opportunity costs of time spent in treatment, but not include any costs related to or any adjustment for the unpleasantness, painfulness or premature death resulting from the interventions. One reason for this recommendation is based on the fact that for most people, it is difficult to disentangle the effect of being ill on their role function, from the effect on their health-related quality of life.

Friction costs are the costs associated with the effects of lost productivity that are borne by others (e.g., administration costs paid by an employer for the replacement of a skillful worker). When it is substantial and relevant, the friction costs should be included in the numerator of the reference case analysis.

Valuing

Both the opportunity costs from a long-run perspective and the value of the resource in its next best alternative use, should be used in the reference case analysis because these are the real costs to the society. In general, if the market were perfect, a prevailing market price is a reasonable estimate of opportunity cost. When market distortion is present, adjustment is required. Charges usually are used as proxies of costs.

The appropriate cost-to-charge ratios for specific services should be used for adjustment of the charges. For many health care interventions, when technology exhibits diseconomies of scale, average costs can be used in the CEA because they are the same as the opportunity costs. When the data on costs come from previous time periods, or when the study is projecting costs for different time periods, costs can vary because of general inflation. In this case, the Medical Component of the Consumer Price Index is needed to correct direct health care costs. For patient time costs, the appropriate age-and gender-specific wage rates, such as data collected in the Current Population Surveys (CPS) of the U.S. Bureau of the Census, can be used as it reflects the estimates of these opportunity costs. For time costs of informal care giving or care taking, valuing the time spent should be based on market service prices.

Measuring

There are two alternatives for measuring resource consumption: micro-costing and gross-costing. The micro-costing, direct enumeration of costs of all inputs consumed in the treatment of the patient, reveals how well the analysis captures real world practices. However, this technique is sometimes not feasible, particularly when patterns of care related to the treatment of interest and its alternative are different, and gross-costing techniques cannot detect such differences. For example, an antibiotic drug in an oral form is compared to an injection form, or a CEA compares various protocols of immunosuppressive agents in transplant recipients. In these cases, measuring the drug received at patient-level is necessary. When such information is not available from the large database, the micro-costing technique should be employed. Gross-costing is based on a sequence of economically significant events associated with the intervention e.g., acute care hospitalization, nursing home care and other institutional services, outpatient care, professional service fees, drugs, outpatient supplies, and durable medical equipment, etc. For these components that the Medicare Program covers, Medicare data sources such as an average DRG payment, the new Medicare Fee Schedule, and abstraction from Medicare Payment database often are used in CEA.

D. Valuing health consequences

For a reference case analysis, the outcome measure should incorporate morbidity and mortality consequences into a single measure, such as the QALY. In general, a QALY is the product of life expectancy adjusted for the index of utility (0-1 scale). Impacts of morbidity on productivity and leisure time should be captured by a preference-based measure for HRQOL yielding the utility outcome (sometimes called quality weight, preference, utility weight, or utility index). The utility must be interval-scaled where the reference point "death" has a score of 0.0 and the reference point "optimal health" has a scale of 1.0. The utility measure should be based on a health-state classification scheme that reflects domains (attributes) that are important for the particular problems under consideration.

In a reference case analysis, a preference measure for HRQL should be a generic one. In addition, the utilities should be derived from a group representative of the community. A sensitivity analysis of the utilities of persons with the condition will be necessary if these utilities are significantly different from community utilities. Adjustment for age, gender, race, and socioeconomic status is also needed because utility may be influenced by the characteristics of the population involved.

E. Section summary

The guidelines proposed by the U.S. Panel on Cost-Effectiveness in Health and Medicine (Gold et al., 1996) include five major recommendations. The use of a reference case analysis, based on the societal perspective that accounts for benefits, harms and costs incurred to all parties, is encouraged. Second, the resources consumed should be valued at their opportunity costs. Third, HRQOL should incorporate the effects of mortality and morbidity on productive time and leisure. The effect of morbidity on productive time and leisure should be captured by a generic health-state classification measuring utility. Fourth, the utility rates should be based on the preferences of the community, for example a representative sample of the community. Finally, costs and health outcomes that occur in the future should be discounted at the same rate. At the present time, although this issue is not new, ideal instruments for measuring utilities are not yet available.

The next section reviews the current status of health-related quality of life based utilities, focused mainly on the development of generic health-state classification systems. The utilities for certain health states in the present CEA are based on the mapping of a generic health-state classification system to the utility that was derived from a community sample.

IV. Health-Related Quality of Life Based Utilities

The standard gamble and time tradeoff methods, when used for primary data collection to measure utilities of health states, have proven to be very difficult to administer. More importantly, psychometric results for these methods vary substantially even in the same group of study patients. Therefore, utility values obtained from different measuring methods may not be directly comparable (Nord, 1996). The rating scale is quite easy, but its psychometrics may be problematic. It has been noted that the method used to measure the subjects' utility values strongly influence the results in CEA (Nord, 1996).

It would be more beneficial if a precise and easier alternative method to obtain utilities in a CEA was available. An example of this is an instrument which simply asks individuals to locate their health state on each attribute in a comprehensive classification scheme. Then each combination of levels is assigned a weight, and summed into a utility index by using a formula based on a community preference survey and multi-attribute utility theory (Feeny et al., 1995). The mapping technique is easy to administer and could be ideal for soliciting preferences as recommended by the Panel. In addition, mapping health states associated with particular illnesses or conditions to the utility would allow users of secondary data sources with access to information about individual's health profile to assign a value of the corresponding utility. As a consequence, this could facilitate comparisons across CEA studies that are designed to inform resource allocation. There is a need for such an instrument that would consist of a set of well-described health states, accompanied with utilities for each state.

Currently, widely accepted generic preference-based measurements for HRQL based on health-state classification systems include Quality of Well-being Scale (QWB), Health Utilities Index (HUI), and EuroQoL (Gold et al., 1996; Drummond et al., 1997). Thus far, the QWB is the most widely applied measure that has been used for QALY computation (Fryback et al., 1997). A more recently developed measure is HUI Mark version 3, which was based on a random sample of the general Canadian population using both the standard gamble and visual analogue ratings. HUI Mark version 3 was constructed to make it an ideal prototype instrument for utility measurement for CEA. However, the scoring formula has been only available since 1999, so it has not yet been as widely applied in patient populations as the QWB. There have been several attempts to develop a weight system based on the most widely used generic health status measure - the Medical Outcomes Study Short Form Health Survey (i.e., SF-36, and SF-12) (Sherborne et al., 1997; Brazier et al., 1998).

The Panel encouraged the scientific community to reach an interim consensus by choosing one of the currently available instruments as a "placeholder" or quasi-gold standard to be used in all status until a better instrument is developed. They have not chosen the placeholder at the present time and one does not appear to be in use.

A. Quality of Well Being Scale

The QWB is a preference-based measure for overall health, and consists of three functioning domains: mobility, physical activity, and social activity. There is also a fourth domain capturing various symptoms and problems. The QWB score intentionally was constructed to represent a judgement of the undesirability of the problem and express it in terms of QALY (Kaplan et al., 1978). Criticisms of the QWB focus on two aspects. First, the QWB is oriented strongly toward physical problems and therefore underrepresents mental health. Secondly, regarding the scale weights, certain more disabled states appear preferable to less disabled ones, and category rating is used to derive weights, rather than magnitude estimate. The newer version of QWB is a self-report with more mental health symptom items and it has not yet been widely used.

B. Utility indices derived from Medical Outcomes Study Short Form Health Survey

There have been at least four approaches for computing utilities from the Short Form Health Survey. The first one is the transformation of SF-36 health profiles into predicted QWB scores (Fryback et al., 1997). Other mapping systems include transformations of the SF-12 health profile into utility scores using equations developed from depressive patients (Sherborne et al., 1998) or the general population (Sherborne et al., 1997). Another approach is the transformation of eight selected items of the SF-36 health profiles into utility scores using the formula based on the sample of health professionals in United Kingdom. (Brazier et al., 1998).

Fryback et al. (1993, 1997) used empirical observations of SF-36 profiles and QWB scores collected in interviews of 1,430 persons during the Beaver Dam Health Outcomes Study, and also 57 persons from a renal dialysis clinic to derive an empirical equation allowing prediction of a QWB score from the SF-36 profile. Using a regression equation based on five of the SF-36 components - Physical Functioning, Mental Health, Bodily Pain, General Health, and Role Physical, these components predicted 57% of the observed QWB variance. However, most of the residual variance unaccounted for by the equation is due to limitations of measurement error in the two instruments, and not a lack in the underlying predictable relationship of the QWB and SF-36 variables. In the cross-validation process, the ability of the equation to predict QWB scores is promising in the general population (R^2=49.5%) and in the sample of renal patients (R^2=58.7%). Problems occur when the profiles are severely limited by floor or ceiling effects of the SF-36 scales, and when applying the equation to data with very low scores in both Mental Health and Bodily Pain subscales.

Table 2.4 Age and health specific mean predicted QWB scores (SD) from SF-36 profiles

Age (years)	General Population	Type I diabetes patients		
		No Complication	Retinopathy only	Other*
< 45	0.82	0.73 (0.07)	0.76 (0.05)	0.70 (0.08)
45-64	0.75	0.68 (0.09)	0.72 (0.09)	0.66 (0.07)
> 65	0.70	0.64 (0.08)	0.62 (0.07)	0.55 (0.05)

* Type I diabetes with diabetic neuropathy or nephropathy alone or any other complications
Source: Wu et al (1998)

Using Fryback et al. (1997)'s equation, Wu et al. (1998) reported the predicted QWB scores of 89 type I diabetes patients from their collected SF-36 profiles. The average predicted QWB scores of the general population and the nine subgroups of these diabetes patients are presented in Table 2.4.

Sherborne et al. (1997) recently has developed an equation to derive utilities from the SF-12 profile using time tradeoff and standard gamble. The preliminary study results suggest some limitations. For example, many patients in the sample (patients visiting their general medical provider; N=18,000) were unwilling to give up any months or years of life for a treatment (Dr. Cathy Sherborne, personal communication). Thus, a large number of people had a utility score of '1'. This makes the derived utility from SF-12 profile seem high. One reason for this might be that the investigators used a simple paper and pencil approach. Sherborne et al. (1998) mapped the weights to the SF-12 health profile in the depressed sample and looked at the differences before and after intervention. The utility measures were very insensitive to the intervention, although the intervention itself had large effects on symptoms and MCS12. In addition, they mapped the SF-36 to the weights developed by Brazier et al. (1998) and found similarly insensitive results to the intervention. These measures may not be usable in cost-effectiveness analyses (Dr. Cathy Sherborne, personal communication).

V. Cost-Effectiveness Analyses in Kidney and Pancreas Transplantation

This section explains how cost-effectiveness studies focusing on patients receiving kidney and/or pancreas transplantation have been conducted. Covered issues are

CEA framework, comparators, target population, health outcomes, cost estimates, discount rates and C/E ratios as reported by previous studies. Sources of the data on effectiveness and costs were scrutinized for appropriateness. Furthermore, conformity with the methods recommended by the Panel of these studies was explored. Only the studies published after the Panel recommendations were released and those providing sufficient details in their methodology used are discussed in detail.

A. CEA of kidney transplantation vs. dialysis

Kidney transplantation has been established as the most cost-effective treatment option for ESRD patients. The high initial cost of the kidney transplant can be recovered within 5 years (Egger, 1992). Whether kidney re-transplantation for those who have graft failure is cost-effective recently has been questioned (Horberger et al., 1997).

Stange and Sumner (1978), and Roberts et al. (1980) reported that cadaver transplants and home dialysis were superior alternatives to in-center dialysis, on the basis of a model with survival rates and synthetic estimation of treatment costs. Stange and Sumner (1978) conducted a CEA with a 10-year time frame and used 5-7% discount rates, whereas Roberts et al. (1980) created a lifetime model where life-years were not discounted. Garner and Dardis (1985) concluded the same results based on a 20-year model with a 10% discount rate, and used two measures of cost: gross social costs (excluded output gains due to treatment), and net social costs (included output gains from both market and non-market activities). The value of output generated by patients was deducted from the gross social costs of health care programs to yield the net social costs.

Eggers used Medicare reimbursement data for cost estimates, and reported that the high initial costs of transplantation were recovered in 4 years for cadaveric transplants and in about 3 years for living donor transplants (Eggers, 1984). In 1992, Eggers updated the cost comparison between dialysis and transplant using a 3% discount rate, and confirmed the same conclusion. The expected total expenditure (1989 U.S. dollars) over a 10 year period was $191,600 for a transplant, compared with $233,300 for dialysis.

None of the studies above incorporated QOL into survivals (i.e., QALY) for the effectiveness measure. All studies found that kidney transplant as compared with dialysis was less costly and offered a better survival rate. It has been widely accepted that kidney transplant recipients experience better QOL than dialysis patients. This suggests that if QALY were used, the results would be even more favorable for kidney transplantation.

Laupacis et al. (1996) reported that kidney transplant, as compared with dialysis, provided a cost saving of about $59,325 for the first year and $394,500 for the second year after transplant (1994 Canadian dollars). The study was conducted using 168 patients on dialysis and followed until 2 years after transplant. The survival, quality of life, and cost data were measured directly from these subjects. A time-trade off measure was used to assess QOL and adjust the survival. The study comprehensively recorded the resources used by patients and their families, and applied the appropriate costs to these data to yield the total cost estimates.

Horberger et al. (1997) studied the impact of kidney retransplant policy by comparing the cost-effectiveness of the retransplant policy with the no-retransplant policy. The target population was patients who were candidates for their first renal transplant. The study was based on the premise that the patients who failed first transplants should not be allowed to enter to the pool of eligible transplant candidates since it would lengthen the expected waiting time for the first transplant candidates. The median waiting time for the first-transplant candidates would decrease from 21 months to 18.5 months, given at 12.1% of the cadaveric transplant candidates who underwent retransplantation were no longer allowed to compete for cadaveric kidneys. The expected gain in QALY associated with shorter waiting periods for the first transplant needs to be compared to the expected losses in QALY associated with having dialyses as the only renal-replacement option if the candidate was among the patients who have failed grafts. Cost estimates and effectiveness on patient and graft survivals were obtained from HCFA and USRDS data sources. The utilities were based on published literature (Torrance, 1987), such as 0.84 for a functioning graft recipient, 0.68 for dialysis, and 0.65 for the first six months following a failed transplant. All costs and future life years were discounted using the rate of 5%. The effects on first transplant candidates with the no-retransplant policy include a 237-day increase in life expectancy, a 47-day increase in QALY, and a $1,210-increase in the lifetime cost of medical care. From the societal perspective, the C/E ratio on first transplant candidates under the retransplant policy compared with the no-retransplantation policy is $9,656 per quality-adjusted life-year saved. The retransplant policy had a more favorable effect on younger candidates.

B. CEA of new immunosuppressive agents and preventive strategies for infectious complications in kidney transplant recipients

Several studies have evaluated cost, effectiveness, and cost-effectiveness of new immunosuppressive agents and strategies to reduce infectious complications. However, few of them used rigorous methods or conformed to the Panel's recommendations. Only reports with meticulous methods are presented here.

A new immunosuppressive agent, OKT3 used for an induction therapy was compared with a conventional triple-drug regimen from a five-center randomized trial among cadaveric kidney transplant recipients (Norman et al., 1993). Shield et al. (1996) reported that OKT3 induction cost $8,335 for each additional year of graft survival based on the model through the expected duration of graft survival. For this study, effectiveness was defined as length of graft survival. The cost data were obtained mainly from the National Cooperative Transplant Study for the charges of organ procurement and routine hospital care for kidney transplant procedure. The Medicare Provider and Analysis Review database was used to determine the median hospital charges of patients who experienced graft rejection, developed an infection, or encountered complications. Finally, charges associated with graft failure or patient death were obtained from a study based on Medicare administrative data. This study placed values on medical resources by applying national average provider charges to medical events and a sensitivity analysis used the Medicare reimbursements. Cost-effectiveness was measured through 5 years of observed follow-up and modeled through the expected duration of graft survival by assuming equal rates of graft failure at 4% in OKT3 induction and conventional groups after 5 years. A 5% annual discount rate was applied to both cost and effectiveness.

Mycophenolate mofetil (MMF) recently was introduced to be used in combination with cyclosporin and corticosteroids for the prophylaxis of organ rejection in patients receiving renal transplant. Sullivan et al. (1997) reported that MMF was more cost-effective than the standard regimen in the first year ($27,807 vs. $29,158) after primary cadaveric kidney transplant, on the basis of the first-year analysis time frame. The primary source of clinical outcomes (i.e., patient and graft survival) and medical resource uses was based on a randomized 14-center controlled trial (N=499) (Sollinger et al., 1995). The perspective is from the societal standpoint, but excludes patient time costs. The cost estimates were obtained from the American Hospital Association for hospital per diem, and HCFA reports for annual dialysis, functioning graft expenditures, and one time graft loss. Costs of outpatient rejection treatment services were estimated from a sample of data obtained from a large mid-western transplantation center. Finally, physician service data was derived from the Medicare Resource-Based Relative Value System fee schedule. The total costs were estimated per year of survival only, not QALYs.

Infectious complications particularly with Cytomegalovirus (CMV) are very common in the transplant recipients under immunosuppressive therapy. McCarthy et al. (1993) reported that the mean cost of successful renal transplant was 2.9 fold higher in patients with CMV disease compared with patients without CMV disease. Prophylaxis with CMV immune globulin (CMV-IG) was shown to be cost-effective for patients at high risk of CMV disease (CMV-positive donor-CMV-negative recipients) in a study conducted by Tsevat et al. (1991). The C/E ratios for administering CMV-IG to each group compared with withholding CMV-IG ranged from $29,800 per life year saved for the highest risk group to $1.68 million dollars for the lowest risk group. The analyses used a one-year time frame and were based on a hospital's perspective that excluded physician fees. The actual cost method (not charges) was based on a cost-accounting software package developed for obtaining actual costs of hospitalization. The effectiveness in preventing CMV-associated disease was based on the trials, and the mortality rates were based on the available data from HCFA. No utility was attached to the life saved. The study assumed the CMV-IG reduced mortality by decreasing the risk of developing CMV-associated disease but did not affect the graft loss and case-fatality rates given CMV-associated disease.

C. CEA of kidney and pancreas transplantation in patients with diabetic ESRD

Few CEA studies have compared KTA and SPK or PAK in the diabetic patients. A CEA of SPK compared to KTA was conducted by the Office of Health Technology

Assessment in 1995. The analysis was based on transplant surgery costs and one-year follow-up costs during the years of 1990-1993. The samples were obtained from selected transplant centers and third-party payers, and these costs varied substantially. Furthermore, the reference case analysis was based on the "middle ground" costs. This study was modeled for a three-year time frame after transplant, which was less than the expected survival period. The analysis assumed kidney graft failure and deaths occurred at the same rates in both SPK and KTA groups. The assigned utility weights for SPK were hypothetical and annual follow-up costs beyond one year after transplantation were not clearly defined in the analysis. QOL preference weights were chosen in favor of SPK, as the weight for KTA at a value of 0.84 was based on a report not specifically tied to diabetic KTA recipients. Incremental costs per QALY gained ratios were based on the preference weight for SPK/KTA ranging from 0.95/0.85, 0.90/0.80, to 0.90/0.75. No discount rate was applied to cost and effectiveness. The study concluded that SPK would be more cost-effective than KTA, if the annual cost of treating hyper/ hypoglycemia in KTA recipients was substantial.

Douzdjian et al (1998) reported SPK was more cost-effective than KTA for a patient with IDDM and ESRD. In the second report using the same methodology, they compared SPK and living-donor kidney transplantation followed by cadaveric pancreas transplantation (Douzdjian et al., 1999). Using a 5-year decision tree model, the expected cost per QALY gained was $27,070 for SPK compared with cadaveric KTA. The living-donor kidney transplantation followed by pancreas transplantation was less cost-effective than SPK (incremental cost-effectiveness ratio: $13,535 per QALY gained). The cost estimates for dialysis and kidney transplantation were based on 1990 Medicare expenditures; these costs were not specific to diabetic patients and were assumed to be similar to the overall recipient population. SPK transplant costs were estimated using the ratio of 1.7 higher than KTA transplant costs. It was not clear how the authors obtained the follow-up cost during the first year of transplantation and thereafter in the SPK group. The post-transplant follow-up costs beyond the first year, excluding insulin therapy, were assumed to be similar in KTA and SPK transplants. Utility weights of various health states were obtained by interviewing 17 SPK recipients, using the standard gamble technique. The utility of the dialysis-free, insulin-free SPK recipient was assigned the value of 1.0. The utility weight for dialysis-free, insulin-dependent was 0.6; for dialysis-dependent, insulin-free, 0.5; and dialysis-dependent, insulin-dependent, 0.4. In fact, all the study patients suffered from diabetic retinopathy and neuropathy on top of uremia nephropathy before transplantation. Thus, the assigned value of 1.0 to the SPK recipients with both grafts functioning may be overestimated from the community perspective. The big difference in the utility weight between SPK and KTA recipients by 0.4 due to insulin dependency may explain the result favoring SPK. Costs and QALYs were not discounted to the present value on both reports.

D. Section summary

Most studies in this area chose the appropriate comparators. The time frames used in most studies had limited horizons and were shorter than graft or patient survival due to lack of available data. Furthermore, costs usually were derived from Medicare payment data or other reliable large databases. Effectiveness was not always adjusted for patient's preference. The preference-weighted effectiveness often was based on hypothetical data, reviewed literatures, or only measured once. No studies used the instruments for measuring preferences that followed the Panel's guidelines. Adjustments for the discount rates of 3% and 5% were not consistently applied.

Recent findings from CEAs conducted in recipients of kidney transplantation introduce several new insights. The kidney retransplant policy with cadaveric donors for those with graft failure costs an additional $9,656 per QALY gained. Both OKT3 and MMF are cost-effective therapies for cadaveric kidney recipients. Prevention of CMV infection by using CMV-IG in the high-risk patient with CMV is worthwhile.

Three CEAs involving SPK have limitations; none of them adhered to the Panel's recommendations. The follow-up cost estimates for the KTA recipients were assumed to be similar to the general population and those for the SPK recipients were not obtained from reliable large data sources. In addition, costs specific to transplant surgery and follow-up costs were not based on the recent or current practices.

VI. Chapter Summary

Management of secondary diabetes complications such as ESRD is very costly and has become the leading economic burden of health care sectors. SPK can enable patients with diabetic ESRD to lead a more normal lifestyle without the burdens of dialysis and insulin therapy. As a consequence of the successful pancreas graft normalizing blood glucose metabolism, SPK could affect on prevention or delay secondary diabetes complications. Improvement in surgical techniques suggests that more widespread applications of SPK are warranted. However, the solid evidence of the long-term health benefits of SPK is not available. Therefore, an investigation of costs after transplantation over a long follow-up time period of SPK and KTA recipients with IDDM can provide a clue to understand the effects of SPK on morbidity and is necessary for a sound CEA of SPK compared with KTA. The investigation can be done using a large health care utilization data source such as Medicare.

Prior studies on the CEA of SPK have not followed the Panel's guidelines. Despite the availability of the Medicare payment database, costs specific to the KTA recipients with type I diabetes and those for SPK have never been reported nor used in the CEAs evaluating SPK. The studies were not based on current information regarding costs and survival data. These analyses were based on a 3 to 5 year-time period after transplantation. As progress in SPK surgery and immunosuppressive regimens have been made in the last decade, generalizability of the results from such studies is limited. In addition, none of these studies used appropriate assigned utilities and discounted future costs and effectiveness to the present value.

The present study examines the cost-effectiveness ratio of SPK as compared to cadaveric KTA with continued insulin therapy over the anticipated lifetime of recipients by using a Markov model. Probabilities of health state transitions to be used for an estimation of life expectancy are derived from the most recent national-level transplant databases. Cost estimates based on Medicare payment data during 1991-1998 are used as the proxy for the opportunity costs. Furthermore, a longitudinal study of SPK and KTA in diabetic ESRD patients provided the primary data on an HRQL-based utility for certain health states. The utilities are predicted QWB scores transformed from SF-36 profiles and adjusted using selectivity-corrected models. QWB is considered a generic health-state classification system that is based on community preferences. All costs and future life years are discounted at 3% per year.

CHAPTER 3

THEORETICAL MODEL

I. Framework of Cost-Effectiveness Analysis

Analysis of the cost-effectiveness of SPK versus KTA in this study follows the guidelines recommended by the U.S. Panel on Cost-Effectiveness in Health and Medicine (Gold et al., 1996). The major issues involve (1) used resources which should be valued at their opportunity costs; (2) HRQOL which should incorporate the effects of mortality and morbidity on productive time and leisure; (3) a generic health-state classification or utility based on community preference; and (4) discounting costs and health outcomes that occur during different time periods (Russell et al., 1996; Weinstein et al., 1996).

Currently, some of the leading transplant centers in the United States rarely perform KTA for type I diabetic ESRD patients (Dr. DER Sutherland, personal communication). In general, SPK is performed unless the patient has contraindications. A multi-centered randomized controlled trial comparing SPK and KTA funded by the National Institute of Health (NIH) is being considered. The present study considers that all patients should receive SPK instead of KTA if SPK is proven to be more effective, and the availability of organs for transplantation is not a concern. As in any randomized controlled trial, the framework for comparison of SPK and KTA is what would happen if the patients were assigned transplant options randomly. Therefore, in the reference case analysis prediction models for transitional probabilities, cost, and utility are based on characteristics in the reference population, i.e., beneficiaries in Medicare ESRD kidney transplant program. This reference population consists of patients age 18 and older who were recipients for primary kidney transplant (as either KTA or SPK) and had type I diabetes as a cause of renal failure during January 1, 1988 to December 31, 1998.

The scenario of this analysis relies on the use of a reference case based on the health care sector perspective. Therefore, this study excluded consideration of certain costs, typically considered direct non-health care costs, including travel costs, patient time costs, and costs associated with care giving during the process of seeking and obtaining transplantation.

The final result is presented as an incremental cost-effectiveness ratio where health outcomes are represented by QALYs and all monetary units of resources used are expressed in 1998-US constant dollars. Effects of the transplantation on the patient's expected length of life and HRQOL-based utility are incorporated in the denominator of the cost-effectiveness ratio.

$$\text{Cost-effectiveness ratio} = \frac{\text{Lifetime costs of SPK - Lifetime costs of KTA}}{\text{QALYs of SPK - QALYs of KTA}}$$

Only direct health care costs incurred by the transplant recipients are included in the numerator. The major cost categories of resources used consist of transplant surgery cost and costs incurred during the post-transplant time period. Evaluation costs during the pre-transplantation period were omitted because the two groups underwent a similar evaluation process to obtain the transplants, and their related costs are similar (Insulin-Free World Foundation, 2000). Monetary value of the loss in economic productivity due to death, and of the loss and impairment in ability to work or to spend time in leisure activities due to morbidity is not included in the numerator. The patient's perception of HRQOL already has taken into account the effects of these losses, therefore, costs associated with the economic loss due to the mortality and morbidity are not included in this study (Weinstein et al., 1996). Cost of resources used and QALYs are modeled through the expected lifetime of patients from the day of admission for transplant surgery.

Transplant recipients encounter uncertain events including risk of graft failure and death throughout their lifetimes. Also, costs and patients' utilities might differ over time. In this analysis, a Markov model, which is state-transition model, is used to estimate lifetime costs and utilities. (Mandelblatt et al., 1996; Sonnenberg and Beck, 1993).

Results from this study can be generalized to patients with type I diabetes and ESRD who are candidates for either SPK or cadaveric KTA with continued insulin therapy. This CEA is limited to the first transplantation of SPK and cadaveric KTA. Any retransplant procedures due to graft failure and pancreas-after-kidney transplant (PAK) is beyond the scope of this study. The rate of pancreas retransplant in SPK was relatively high in the past. However, at the present time, pancreas and kidney graft failure rates in the recipients of SPK have been reduced dramatically and come close to the kidney graft failure rate in KTA.

Since data on costs are obtained during different time periods, time preference becomes an issue. In order to eliminate effects of economy-wide inflation, all current dollars are converted into 1998-US constant dollars by using the medical care component of the Consumer Price Index. To take into account societal preferences for present over future events, both costs and QALYs are discounted to the present values using the annual discount rates of 3% for the reference case analysis. The Panel on CEA has recommended the investment rate of 3% be used as the discount rate, and a 5% discount rate should be subject to a sensitivity analysis because it is a prevailing norm.

The Panel on CEA has recommended the use of generic measures of HRQOL, not disease-specific measures in order to facilitate comparability across CEA studies (Weinstein et al., 1996). This study used a generic HRQOL measure, the 36-item Health Status Survey Short Form (SF-36), can be transformed into the predicted QWB scores by using the equation developed by Fryback et al. (1997). The predicted QWB scores are used as the assigned utility for three health states. The chosen SF-36 measure reflects the outcome domains relevant to the chronic illness in this study population (Wu et al., 1998; Gross et al., in press). As part of the Beaver Dam Health Outcomes Study, Fryback et al. (1997) derived an empirical equation based on community survey of SF-36 and QWB scores. Detailed description of the transforming equation is explained later in the Methodology Chapter.

II. Health State Transition Model

Estimation of expected lifetime costs and QALYs is based on a Markov model, or state-transition model, that allocates, and subsequently reallocates, members of the transplant cohorts among several health states. Diabetic ESRD patients who received transplants may remain alive with a functional graft, develop graft failure (kidney for KTA recipients, and kidney or pancreas or both for SPK recipients), or die of new or existing complications of diabetes or of other causes. Even though retransplant due to graft failure is not uncommon, this treatment choice was not included in this already fairly complex models. This analysis counts each year as a cycle during which a finite set of three health states for KTA and five health states for SPK are possible (Figures 3.1 and 3.2). Possible transitions among health states in a cycle are depicted by the arrows. The recursive arrows represent the probabilities that patients would remain in the same health state at the end of each cycle.

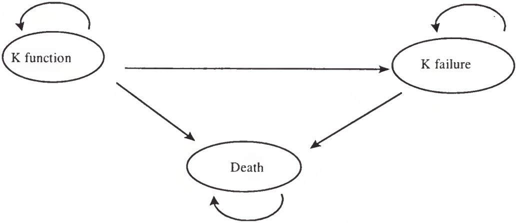


Figure 3.1 Health-state transitions for KTA

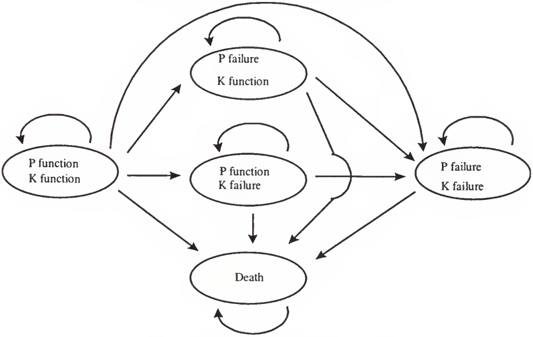


Figure 3.2 Health-state transitions for SPK

P: pancreas graft, K: kidney graft

There are three health states for KTA: dead, K functioning, and K failure. Transitional probabilities for KTA recipients with K graft functioning status include the probabilities to: a) death; b) K failure; and c) remaining with K functioning. Transitional probabilities for the KTA recipients with K graft failure include the probabilities to: a) death; and b) remaining with K failure. For SPK recipients who had both pancreas and kidney graft functioning status, transitional probabilities include the probabilities to: a) death; b) staying P and K functioning; c) P failure only; d) K failure only; and e) P and K failure. Transitional probabilities for SPK patients with only P graft failure include the probabilities to: a) death; b) staying P failure only; and c) P and K failure. In summary, the possible health states for SPK include death, both P and K functioning, P failure only, K failure only, and both P and K failure.

Probabilities of the transitions between health states are derived from patient and graft survivals conditional on each health state in a yearly cycle basis. Information on the patient and graft survival rates comes from time-to-event data from the national transplant registry.

III. Models for Transplant Choice and Utility Outcome

A. Selection bias on an estimation of treatment effect

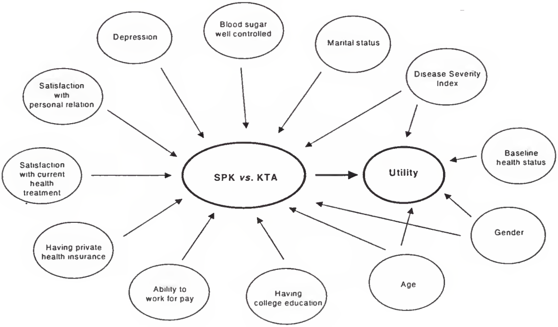
Type I diabetes is a chronic illness that can influence the utility of an individual because the treatment is burdensome and the complications can be debilitating and life threatening. In general, transplant choice depends on an individual's evaluation of several differences between SPK and KTA. SPK offers no more insulin therapy but has more risks. SPK may also have impact on secondary diabetes complications. The effect of transplant choice on costs and outcomes may be confounded by some factors that are unobservable or unmeasured. Many possible confounders were not available for the analysis of costs and outcomes in the present study. For instance, individual's prognosis or susceptibility to developing diabetes complications may affect the transplant choice and correlate with the utility. Individuals who choose SPK may prefer a more aggressive medicine style (Daneman and Frank, 1998). SPK candidates may differ from KTA candidates in their attitudes toward health care and illness. These factors are likely to be related to the transplant choice and the outcomes measured after receiving transplantation. If the analysis was not adjusted for unobservable error components affecting choice of transplant that are correlated with the unobservable error components in the utility estimation model, this can bias the estimates of treatment effect of SPK vs. KTA. The problem is referred to as selection bias.

For two health states: KTA with kidney graft function and SPK with both grafts function, the present study obtains the utilities, predicted QWB scores from a longitudinal QOL study, which provided some pre-transplant characteristics associated with the nature of the patient selection process to seek transplant choice. This information allows us to correct the self selection bias (Mullahy and Manning, 1996). However, there was no information at the pre-transplant stage available for correcting self selection bias for costs and survivals.

B. Determinants of transplant choice

The present study explicitly models the determinants of a patients' transplant choice (Figure 3.3).

Figure 3.3 Models for transplant choice and utility outcome



Based on the literature review, there have been no studies examining patient preferences for SPK or KTA. Therefore, no direct evidence of factors affecting the transplant choice is available. However, literature on psychological aspects in patients with IDDM offer clues on the reasons why an individual may seek SPK (Jacobson, 1996; Wainwright et al., 1999). Logically, patients who have well-controlled their blood sugar over years and still experienced diabetes complications like uremia nephropathy, as in the study sample, are likely to seek SPK as a new treatment option that may offer the way to prevent further progressive complications. In addition, dissatisfaction with conventional diabetes treatments (i.e., insulin, diet and lifestyle restrictions) would increase patients' willingness to seek SPK. Older patients or patients experiencing more severe illnesses seem to be reluctant to choose SPK because of an awareness of the increased short-term risks of SPK-induced morbidity. Problems with personal relationships due to diabetes, for example, negative impacts on spouse or family might influence patient's decision to receive SPK. Low enthusiasm for future life reflected by depression may explain the preference for KTA over SPK. Another important issue may be associated with the patient's financial status and this can be reflected by their health insurance, ability to work for pay, and education.

C. Factors affecting utility outcome

Factors related to lower utility for persons with type I diabetes include less education, lower income, older age, being female, number of diabetes complications and lower levels of physical activity have been reported (Glasglow et al., 1997). In the present study, the utility outcome for two health states: KTA with graft functioning and SPK with both graft functioning are represented by a predicted QWB score. The QWB is a preference-based measure for overall health (i.e., not the true utility in an economic sense). Thus, variations in observed utility in this study are explained as the effects of transplants and a set of underlying factors including patient characteristics of age, gender, baseline physical health measured by Karnofsky scale, and Diabetes Severity Index (Figure 3.3). As observation of the utility is conditioned by the transplant choice in that selection into SPK versus KTA is not random, the inclusion of the observed covariates in the utility equation is not sufficient to control for potential correlation in the unobservable variations between transplant choices and the utility. The transplant selection model provides the risk of not receiving a particular transplant, given that treatment was an option, and these estimated probabilities are included in the utility outcome equation to correct selection bias.

D. Justification of the selectivity-corrected model

This study used the selectivity-corrected model (Barnow et al., 1980) for estimation of the transplant effect on utility. It is essential to use this model because important unobserved variables, such as clinical severity and prospects for diabetes progression, could motivate a patient to choose a transplant option and affect their utility outcome after transplant. The true effect of SPK over KTA in the utility equation can be revealed by explicitly adjusting for a selection variable obtained from modeling the patient's decision on transplant choice.

This study chooses variables to be specified in transplant choice and utility models based on the theoretical background stated above (Figure 3.3). In summary, the transplant choice model included variables capturing: (1) an evaluation of pretransplant health treatment (degree of agreement in blood sugar well-controlled, satisfaction with current health treatment, and Diabetes Severity Index); and (2) factors related to attitude toward risks and benefits of the transplant choice (depression score, satisfaction with personal relationships, marital status, ability to work for pay, college education, having private health insurance, and patient age). The utility estimation model includes the type of transplant received, patient age and gender, Diabetes Severity Index, and Karnofsky Performance Index. Age and diabetes severity are explanatory variables that overlap in both models. This study includes two variables in the choice equation: marital status and college education (measured at pretransplant period), which are excluded from the utility equation. It is likely that a married individual would tend to seek SPK in light of anticipation of benefits from the pancreas transplant that can reduce burdens to the spouse. Likewise, a college-educated person is potentially more inclined to aggressive treatment like SPK because of greater appreciation for medical progress. By nature of these two variables, they are exogenously predetermined, hence, they do not depend on clinical severity or progression of diabetes complications. In addition, lack of statistical significance of the two variables in the utility equation supports the assumption.

As previously mentioned, leading transplant centers recently have accepted SPK as a routine practice for type I diabetic ESRD patients (Dr. DER Sutherland, personal communication). This study predicts the effects of SPK and KTA on utility under a scenario that everybody in the reference population receiving SPK versus everybody receiving KTA as in a randomized trial setting. Therefore, the selectivity-corrected estimation of the effects of SPK, as compared to KTA, on the utility outcome in this scenario is based on the whole sample model.

CHAPTER 4

METHODOLOGY

I. Data Sources

The principal data sources of patient and graft survivals and health care costs for this study come from two transplant registries and Medicare billing records. The data source, for utility estimates conditional on health states with respect to graft status for quality of life adjustments in the model, is a longitudinal QOL study (Gross et al., in press) and other published literature, which is described in detail in Section 5.

Medicare End Stage Renal Disease (ESRD) Program Management and Medical Information System (PMMIS) provided a file with information on kidney transplant patient survival and kidney graft status. The United Network Organ Sharing (UNOS) provided a file with data on pancreas graft status specific to SPK recipients. Medicare claims data for cost estimation was extracted from the Medicare National Claims History (NCH) database by using the Health Insurance Claims (HIC) number in the Medicare ESRD kidney transplant file as the unique identifier. However, these kidney transplant data were the universe of kidney transplant procedures performed for all Medicare beneficiaries regardless of their pancreas transplant status. Therefore, separation between KTA and SPK in the kidney transplant data set was required for the purposes of this study.

During the time frame of this study, Medicare did not cover costs associated with pancreas transplant surgery even when performed with a kidney transplant covered by Medicare. SPK recipients who were not Medicare beneficiaries tended to have different degrees of accessibility to health care when compared with KTA recipients who continued with insulin therapy and Medicare enrollees. Therefore, only the UNOS-registered recipients of SPK who have been also enrolled in the Medicare ESRD Program were included in the study sample. However, the SPK transplant data from UNOS did not contain complete temporal records on patient survival and kidney graft status. Information on the non-reported patient survival and graft status was recovered from the patient-matched ESRD kidney transplant file.

Table 4.1 presents patient inclusion criteria and variables required from the three major data sets used in determination of transition probabilities and cost estimates in this study. The study patients include those who underwent either primary cadaveric KTA or SPK between January 1, 1988 and December 31, 1998 and were enrolled in the Medicare ESRD Program. All patients had type I diabetes as a cause of renal failure and were 18 years of age or older at the time of transplant surgery.

Data files created by HCFA such as the ESRD kidney transplant data file and Medicare claims data file contain the HIC number of all Medicare beneficiaries for every record. This HIC number can be linked among different HCFA-generated data files. The first nine characters are based upon the Social Security number (SSN) of the enrollee whose benefit is being relied upon (typically the recipient or their spouse). The tenth and eleventh characters are based on eligibility status of the individual enrolled in Medicare, categorized on the basis of an ‘equated beneficiary identification code’ system in Medicare claim records. A Cross-Reference File was created by HCFA to provide the corresponding equated and unequated HIC numbers of individuals needed to link the Medicare ESRD kidney transplant file and Medicare Claim data files.

Table 4.1 Patient inclusion criteria and variables required

Data source: Kidney Transplant Data File from Medicare ESRD Program
Time period: January 1, 1988 – June 30, 1999
Inclusion criteria:

1. Age ≥ 18 years at time of transplant surgery
2. Patients who had type I diabetes (ICD-9CM: 250.01) as a cause of renal failure
3. Patients who received primary cadaveric kidney transplants (i.e., no prior kidney transplant)

Variables:

1. Demographic characteristics: date of birth, gender, and race
2. Cause of renal failure
3. Number of kidney transplant procedure(s) received
4. Date of transplant and type of organ donor for kidney (cadaveric only)
5. Date of kidney graft failure
6. Date of death
7. Unique identifier (i.e., Health Insurance Claim or HIC number)

Data source: SPK Transplant Data File from UNOS
Time period: January 1, 1988 – June 30, 1999
Inclusion criteria:

1. Aged ≥ 18 years at time of transplant surgery
2. Patients who had received primary cadaveric simultaneous pancreas-kidney transplants (i.e., no prior pancreas or kidney transplant)

Variables required:

1. Demographic characteristics: date of birth, gender, and race
2. Age at onset of type I diabetes
3. Number of previous transplant procedure(s) received
4. Date of transplant and type of pancreas transplant surgery (SPK only)
5. Type of organ donor for pancreas and kidney transplant (cadaveric only)
6. Date of pancreas graft failure
7. Date of kidney graft failure
8. Date of death
9. Unique identifier (i.e., Social Security Number (SSN) or HIC number)

Data source: Medicare Claims Data
Medicare claim data used in this study consisted of the following data files:

- Medicare Provider Analysis and Review (MedPAR)
- Home Health Agency Standard Analytical File
- Hospice Standard Analytical File
- Outpatient Standard Analytical File
- Physician/ Supplier Part B Standard Analytical File
- Durable Medical Equipment Standard Analytical File

Time period: January 1, 1991 – December 31, 1998
Inclusion criteria:

1. Age ≥ 18 years at time of transplant surgery
2. Patients who had type I diabetes (ICD-9CM: 250.01) as a cause of renal failure
3. Patients who received primary cadaveric kidney transplants (i.e., no prior kidney transplant)

The process was done by using the finder file with HIC numbers of the set of all patients included in the kidney transplant data file from Medicare ESRD Program as described above matched with Medicare National Claims History Database

Table 4.1 (Continued)

Variables required:

1. Demographic characteristics: date of birth, gender, and race
2. HMO enrollment
3. Months of coverage by Medicare for Part A and Part B
4. Dates of obtained health care services (start and end dates)
5. Type of provider
6. Diagnoses and Procedures: ICD-9CM or CPT corresponding to healthcare services obtained
7. Dollars of payments: Medicare payment, non-Medicare primary payer payment, coinsurance, deductible, 'pass through' payment
8. Unique identifier (i.e., HIC number)

The Medicare ESRD-linked UNOS SPK database allowed us to identify SPK recipients who were enrolled in the Medicare ESRD Program. However, the UNOS SPK file mostly contains the individuals' SSN rather than their HIC numbers. HIC numbers for individuals in the UNOS SPK data were recovered by matching SSN and date of birth with the Vital Status file (extracted from the Enrollment Database, EDB[1] at HCFA). The Vital Status-matched SPK file was then merged by HIC number with the Cross-Reference file. The matched cases were identified as the SPK recipients who were enrolled in Medicare ESRD Program. The unmatched cases were a set of potential KTA recipients.

In order to obtain KTA recipients with continued insulin therapy from the Medicare ESRD kidney transplant data, two approaches were taken. First, UNOS data on solitary pancreas transplant, including pancreas after kidney transplant and pancreas transplant alone, were merged with unmatched cases in the ESRD kidney transplant data using the same process as above and excluded from further consideration. Second, the remaining unmatched cases were excluded if they had any Medicare claims with an ICD-9CM of pancreas transplant or pancreas graft rejection episode. The final unmatched cases in the ESRD kidney transplant data file were identified as KTA recipients continuing with insulin therapy.

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[1] The EDB is the current HCFA repository of enrollment data of persons who've ever enrolled in Medicare.

The approach to case finding detailed above resulted in 8,893 KTA recipients and 3,700 SPK recipients who were enrolled in the Medicare ESRD Program during January 1, 1988 to December 31, 1998 and met the inclusion criteria of this study. The KTA recipients with continued insulin therapy included in the analysis of this study made up 67% of the total kidney transplant recipients who had primary cadaveric renal transplant and had type I diabetes as the cause of renal failure (N=13,261). In the other words, 33% of the kidney transplant recipients in Medicare ESRD had a certain type of pancreas transplantation in addition to kidney transplant, and SPK accounted for 82% of these. The SPK study sample represents 56% of all UNOS-registered recipients of cadaveric SPK as a primary transplant during this time period. All study samples were later used in a survival analysis in order to estimate transitional probabilities of patient survival and graft survival rates. Subsets of the study samples in both study groups that met the criteria of full-year Medicare enrollment in non-managed care were then merged with Medicare claims in order to estimate annual costs conditional on graft functioning or graft failure health states.

II. Markov Model

Transplant recipients encounter uncertain events including risks of graft failure and death throughout their lifetimes. The transplant recipients of this study had type I diabetes and their transition probabilities, utilities, and health care expenditures are likely to change with time according to the nature of this chronic disease. A conventional decision tree does not capture such dynamic quality and can model only fixed time horizons. In the simple decision tree, when the probability to move to another health state changes with time, the transition to another health states is usually assumed to occur at the midpoint of the time horizon. Sometimes, a time-averaged probability is employed, but it may be difficult to derive if the probabilities change in a nonlinear fashion.

In this analysis, a Markov model rather than a simple decision tree model was used to overcome the above limitations. A Markov analysis performed with current computer software program provides a flexible and convenient means of modeling long-term scenarios. A Markov process is a modeling technique, and details are described elsewhere (Naimark et al., 1997; Sonnenberg and Beck, 1993). Lastly, Markov modeling has been used to estimate outcomes in numerous cost-effectiveness studies (Gold et al., 1996).

In this study, transitions among the health states are assumed to follow a Markov process where the transition probabilities depend only on the health states considered in the current cycle (i.e., Markovnian assumption). The probabilities of transitions to the current state of death consist of varying probabilities of death conditional on the graft status (i.e., functioning and failure) before death.

Simulation of the Markov process is performed until all cohorts are absorbed into the health state of death. Differences in the number of patient cohorts surviving to the next cycle between the two transplant groups results from variations in the transition probabilities for each health state. The average number of the survived cohorts over the total number of simulated cycles yields years of life expectancy for each transplant group. In order to estimate lifetime costs and adjust the life expectancy with quality of life, annual costs and utility weights are assigned to each corresponding health state in a given cycle. This analysis was performed by using DATA version 3.5 computer software (Williamstown, MA).

III. Computation of Transitional Probabilities: Death and Graft Failure Rates

The two separate transplant data sets of KTA (N=8,893) and SPK (N=3,700) recipients were used to estimate probabilities of death and graft failure conditional on each of the six defined health states. Estimation of these transitional probabilities was based on 'time-to-event' patterns of patient and graft survivals. The conditional probabilities of death and graft failure were plugged into each yearly cycle in the Markov model to estimate life expectancy for KTA and SPK recipients. Patient subgroups receiving transplant surgery between 1994 to 1998 provided the transitional probabilities for years 1-4 following the beginning health state. The probabilities specific to years 5-10 were based on subgroups with transplant surgery between 1988 to 1993. The transitional probabilities for the remaining cycles were assumed to be equal to the probability in the last available year, unless a more appropriate approach was needed.

For the health state of both pancreas and kidney grafts functioning, graft failure rates were based on the time period from the date of SPK transplant surgery until the first graft failure. Similarly, the time period between the first graft failure and the second graft failure provided the basis for the second graft failure rate conditional on the first graft failure health state. For SPK recipients, pancreas graft failure rates were calculated for those who had both functioning pancreas and kidney grafts and those who had first kidney graft failure. Similarly, kidney graft failure rates were computed for both functioning pancreas and kidney grafts and for those who had first pancreas graft failure. Right censoring of graft survival was defined at date of death, date of loss of follow-up (as indicated in the UNOS data for pancreas graft status of SPK recipients), or at the end of observation period (June 30, 1999). Patient death rates conditional on graft functioning status were estimated from the date of transplant surgery until death with right censoring for the end of observation period (June 30, 1999). For KTA recipients, the same process was followed.

In the transplant medical community, graft failure rates also count death as an event regardless of the patient graft status at the time of death. This method of calculating probabilities of graft failure rates, however, cannot be applied to this study because graft failure and death need to be the mutually exclusive events in a Markov model.

As stated earlier in Chapter 4, probabilities of the transition between health states for each year are derived from patient and graft survivals conditional on each health state. Estimated death rate and graft failure rate from time-to-event data at each year following the beginning of each health state are used as the transitional probabilities in the Markov model. To control for the differences in patient and graft survivals across demographic mix of the recipients of SPK and KTA, a Cox proportional hazards model was used for calculation of coefficient estimates adjusted for age, gender, and race characteristics, and an estimation of baseline hazards of the yearly study sample.

Under the Cox proportional hazards model, the hazard at failure time t is assumed to be $h(t) = h_0(t)e^{X\beta}$, where $h_0(t)$ is the baseline hazard at time t. The Cox model provides estimates of β, but provides no direct estimates of $h_0(t)$. As proposed by Kalbfleisch and Prentice (1980), an estimate of the baseline hazard for the ordered failure time with index j (t_j) is recovered by $h_0(t_j) = 1 - \alpha_j$, where α_j is the solution of

$\sum_{k \in D_j} \frac{e^{X_k \beta}}{1 - \alpha_j^{e^{X_k \beta}}} = \sum_{l \in R_j} e^{X_l \beta}$ where D_j is the set of failure observations at t_j and R_j is the set of at-risk observations at t_j.

For each follow-up year, the mean value of the product between the adjusted baseline hazards and exponential of the linear prediction based on age, gender, and race of the reference population, is used as the transitional probability for each health state. The transitional probabilities are estimated until the number of patients available for follow-up is less than 30.

The period of time an individual spent in each health state was determined from temporal records on transplant surgery, patient and graft status from the ESRD kidney transplant data file, and the UNOS-matched ESRD pancreas-kidney data file. Specifically, time periods after transplant surgery until graft failure, death, or censor date belong to a graft functioning health state; and those between graft failure and death or censor date belong to a graft failure health state. In order to estimate annual total costs associated with each health state, these defined health state periods that cover the beginning and the end of time periods of relevant health care provisions would indicate the annual total costs conditional on the given health state of the patient-matched claim files.

IV. Estimation of Costs

Since charges often are inflated and sometimes are not a good proxy for costs (Gold et al., 1996), in this study, major estimates of costs for each year after transplantation and for each health state were obtained from Medicare claims data. Medicare is an excellent source to use for obtaining cost data on kidney transplant (Eggers, 1994). Annual total costs were calculated using the summation from all claim files including hospital inpatients and skill nursing facilities, home health agencies, hospices, outpatients, physician/suppliers, and durable medical equipment.

Medical expenditures, including the amount paid by Medicare and any additional amounts related to beneficiaries' deductible and coinsurance, for whom Medicare is the primary payer are used as a proxy for direct medical care costs in this study. Medicare coverage does not include most nursing home services or prescription drugs that are self-administered. Therefore, costs associated with insulin therapy are added when necessary according to the health states that do not have pancreas graft functioning. Costs associated with maintenance immunosuppressive therapy are not added because these costs are similar between SPK and KTA recipients and under this CEA they received the same Medicare benefit package for the immunosuppressive drugs.

A. Algorithm handling Medicare claims data

Persons with full-year coverage for both Part A and Part B and who have never enrolled in HMOs during the twelve-month period were included in this study. Verification of the coverage status was accomplished by using HCFA Denominator (Medicare eligibility) files for each calendar year. The enumeration of costs was based on total payments for transplant recipients who had Medicare as the primary payer (USRDS, 1995). This study did not include those with Medicare as the secondary payer to other insurance policies since certain claims might not be paid and reported by Medicare.

Including claims, with Medicare as the secondary payer, would underestimate the true expenditures per transplant recipient. Those who had dual eligibility under Medicare and Medicaid were not identified and were not excluded from this study. However, deductible amounts for hospitalization and nursing home care, which were covered by Medicaid were made available in the Medicare claims records.

Medicare was considered the secondary payer for kidney transplant patients under the following conditions:

1. Any claims contained payments from a non-Medicare primary payer
2. Inpatient claims contained zero Medicare payments for transplant surgery
3. Annual total of Part B Medicare payments equaled zero.

Persons were excluded if the first claim during the first year after transplant surgery had zero Medicare payments for hospitalization from MedPAR, or if annual Medicare total payment from Part B including outpatient, physicians/suppliers, and durable and medical equipment was zero.

For face validity, cases with an annual amount above $ 1,000,000 for total payments were considered invalid and, hence, were not included for cost estimation. Also, cases with annual amount of Part B and outpatient services of zero payment were excluded.

Data elements from each of the Medicare claims that were used to generate total costs for an individual beneficiary were selected as follows. Costs associated with care provided in hospitals, skilled nursing facilities, and outpatient settings were derived from the summation of Medicare reimbursement amounts, deductible liabilities, co-insurance, and pass through amounts (in case of inpatient care under prospective payment system).

Costs related to physician and supplier claims and also durable medical equipment claims were equal to either allowed charges (for claims with assigned providers) or submitted charges (for those with non-assigned providers). The costs associated with care provided by home health agencies and hospice consisted of payments from Medicare.

B. Components of costs for each health state

For the health state of kidney graft function in KTA recipients and the health state of both pancreas and kidney graft function in SPK recipients, the first year expenditures include transplant surgery cost and other health care follow-up costs that incur within the first year following transplantation. The total annual expenditures of the second year after transplant and thereafter include only follow-up costs for a maintenance graft therapy and costs for treatment of complications such as graft rejection episodes, diabetes complications, or other health problems.

For payments in each year following health states of any graft failures, transplant surgery costs are not added, because a patient in the graft failure health states moved from the graft functioning health states. For the health states of kidney graft failure, the expenditures include dialysis and other treatments for ESRD, diabetes complications, and other health problems. For the health states of only pancreas graft failure, the same kinds of expenditures are included, however, costs related to renal replacement therapy were excluded. In SPK recipients, health states with only one graft failure (i.e., either kidney or pancreas) need to include maintenance treatment for graft functioning of the graft that is still functioning.

C. Transplant surgery costs

Transplant costs during hospitalization for transplant surgery (transplant stay period) are based on charges for organ acquisition, hospitalization costs, and physician fees (Eggers, 1994). During the time frame of this study, Medicare did not cover the additional expenditures associated with pancreas transplant surgery for SPK recipients, as previously mentioned. Therefore, the medical expenditures of hospitalization for transplant surgery in MedPAR file of the SPK group reflects only expenditures related to kidney transplant surgery alone.

In this study, costs of transplant surgery for SPK recipients were estimated by upward adjustment of the costs of their kidney transplant surgery obtained from MedPAR files. The ratios for hospitalization, organ acquisition, and surgeon fees used in this study were derived from different sources. Furthermore, the ratio for adjustment of hospitalization was derived from the estimated recent costs of hospitalization for transplant surgery of SPK and KTA retrieved from a transplant center's hospital itemized billing records. The patient selection criteria are shown in Table 4.2. Patients were eligible if they received either a primary cadaveric KTA or SPK before March 1999 (working backwards until the required numbers of patients, approximately 30 of them in each group were reached). Thirty-two SPK recipients who met the study criteria had the transplant surgery between January 1998 and March 1999. Twenty-seven KTA recipients with type I diabetes had the transplant surgery between January 1996 to March 1999. Cost-to-charge ratios of 50% were then applied to the charges of hospitalization. The ratio of 1.6113 (SPK: KTA) was obtained, and was then used to multiply the costs of hospitalization for kidney transplant surgery of SPK recipients retrieved from MedPAR files.

Table 4.2 Inclusion criteria for sample patients providing transplant surgery cost ratio

KTA

1. Age 18 or older
2. Patients receiving primary kidney transplant (i.e., no prior kidney transplant)
3. Patients receiving cadaveric kidney donor organ
4. Patients who had type I diabetes as a cause of renal failure
5. Patients not receiving multiple organ transplants
6. Patients discharged with kidney graft function

SPK

1. Age 18 or older
2. Patients receiving primary simultaneous pancreas-kidney transplant (i.e., no prior pancreas or kidney transplant)
3. Patients receiving cadaveric pancreas and kidney donor organs
4. Patients who had type I diabetes as a cause of renal failure
5. Patients not receiving multiple organ transplants other than simultaneous pancreas-kidney transplant
6. Patients discharged with both pancreas and kidney graft function.

Organ acquisitions were not consistently included in the MedPAR files. Most kidney acquisition charges are allocated to non-ESRD beneficiaries as ‘pass through’ payments. Therefore, we used the average kidney acquisition payment of $25,013 (1994 U.S. dollars) provided by HCFA for the KTA group. The organ procurement for pancreas and kidney were estimated by upward adjustment of the payment for kidney acquisition with a ratio of 1.547. This ratio came from the same source as the transplant surgery costs described above, and the cost-to-charge ratio was not applied to organ acquisition. The payments for organ acquisition were assumed to be the same across all patients. In summary, for a reference case analysis we added $28,699.75 for kidney acquisition and $44,398.51 (1998 U.S. dollars) for pancreas and kidney acquisition to transplant surgery costs obtained from MedPAR files. However, the amount of actual charges for each type of organ acquisition is set arbitrary by the regional Organ Procurement Organizations

(OPOs). Therefore, the range of fees of organ acquisition across OPOs is subject to the sensitivity analysis.

The surgeons' and anesthesiologists' fees specific to kidney transplant surgery in both KTA and SPK group were obtained from Physician/Supplier Part B files. For pancreas transplantation (for the SPK recipients), these fees were increased by $2,300 to the total Physician/Supplier Part B payment of the first year of transplant. The Medicare fee schedule available in January 2000 had a national average payment for surgeon fees of $1,958.27 for pancreas transplant. We estimated that the fees for the surgeon and anesthesiologist that were not covered by Medicare and not recorded in the Medicare claim were about $2,300 (1998 U.S. dollars).

D. Follow-up costs

Even though Medicare ESRD program typically did not pay for the additional pancreas transplant surgery before July 1999, SPK recipients were still eligible for the same Medicare coverage as KTA recipients were. Both received up to three years of follow-up care following a successful kidney transplant.

Major cost components during the post-transplant time period consist of immunosuppressive therapy and treatments of rejection and other complications (Eggers, 1994). The annual costs after transplantation were based on total expenditures as described previously. All annual expenditures were retrieved with respect to the health states, and the values assigned into the Markov model were the means of predicted values of the reference population adjusted for age, gender, race, year of transplant or year of beginning the health state, and health states.

All cost components according to health states and their data sources are summarized in Table 4.3. Medicare began to cover maintenance immunosuppressive therapy for ESRD beneficiaries receiving kidney transplant for a period of three years after transplant in July 1, 1995. However, Medicare did not cover outpatient prescription drugs such as insulin and for the data used in this study, Medicare did not cover diabetes monitoring kits or diabetes education management programs. Therefore, the cost of convention insulin therapy (DCCT, 1995) was added to the annual costs of the KTA group and the SPK recipients with pancreas graft failure. The amount of $1911.55 based on 1998 U.S. dollars was used in this study.

Table 4.3 Cost components (to be converted into 1998-constant dollars) and data sources

Health states and cost components	Data sources
Transplant surgery costs	
KTA	Medicare claim data
SPK	Medicare claim data modified
Annual costs at years 1-3 post-transplant time period:	
KTA	
Surviving with K function	
Follow-up payments*	Medicare claim data
Conventional Insulin therapy	DCCT
Surviving with K nonfunction	
Follow-up payments*	Medicare claim data
Conventional Insulin therapy	DCCT
SPK	
Surviving with P function and K function	
Follow-up payments*	Medicare claim data
Surviving with P function and K nonfunction	
Follow-up payments*	Medicare claim data
Surviving with P nonfunction and K function	
Follow-up payments*	Medicare claim data
Conventional Insulin therapy	DCCT
Surviving with P nonfunction and K nonfunction	
Follow-up payments*	Medicare claim data
Conventional Insulin therapy	DCCT

*Follow-up payments include total expenditures for costs associated with diabetes complications, monitoring and immunosuppressive agents for maintenance of graft functioning, treatment of rejection episodes, and dialysis in cases with kidney graft failure

K = kidney graft, P = pancreas graft

E. Model for predicting costs

In this study, the cost conditional on health state, demographic status, and year of the beginning of health state is estimated using cross-sectional observations available in each of the follow-up years. For each health state, the number of patients left in a given follow-up year decreases as the year increases. A health state contributes the cost data for the estimation until the total number of patients in a given year less than 30.

Observed transplant surgery costs, length of hospital stay for transplant surgery, and annual total costs were abstracted from the set of data that was based on non-random allocation of transplant procedures. Patient case mix may not be comparable across health states. In general, Medicare claims data contain observations on patient characteristics and payments at the individual patient level. In this study, the above health care utilization conditional on health state was estimated using a model that accounted for the distribution patterns of cost associated with covariates (Blough, 1999). Explanatory variables including age, gender, race, health state, and year of transplant surgery or year at the beginning of health state with graft failure were used in the estimation model.

There are two primary concerns about the statistic distribution of costs. First, annual total cost data in this study contained only the non-zero values, including routine physician visits, hospitalization costs, and other possible values. These values exhibited positive skewness. Secondly, the variance of cost might not be constant (i.e., heteroskedastic) across health states and covariates in the model. Cost estimates from the widely used log-transformed linear regression model would be biased in the presence of heteroskedasticity (Manning, 1998). This is the case in the preliminary analysis of this study when log-transformed linear regression models were used. In order to identify the underlying distribution of the costs, distribution of residuals of expected costs conditional on health states was examined (Manning, 1998). For transplant surgery cost data, the variance was approximately the cubic of mean value and the inverse Gaussian distribution was assumed. The variance of length of stay was about the square of mean and the gamma distribution with log link function is used for the prediction model. The variance of annual total costs was about the square of mean value for almost every year. Hence, the estimation of annual costs assigned into the Markov model was based on generalized linear model that uses gamma distribution with log-link function. The mathematical approach was described elsewhere (Blough et al., 1999).

The resulting coefficient estimates from GLM are used for a prediction of annual cost associated with each health state. Based on the log function model, the predicted value of annual cost for each individual is equal to the exponential of a linear prediction. Furthermore, it was based on the mix of age, gender, and race of the reference population representing the health technology of 1997 to 1998. The mean value of the predicted annual costs specific to each health state available in each follow-up year was then assigned to the Markov model.

V. Estimation of HRQOL-based utilities

A. Utilities assigned to Markov model

Table 4.4 provides the data sources for utilities assigned to the Markov model. The utility weights assigned to the health states of both pancreas and kidney graft function in the SPK group and kidney graft function in KTA group were derived from SF-36 data collected by Gross et al. (in press). The SF-36 health profiles then were transformed into the predicted QWB scores (Fryback, 1997). These predicted QWB scores, which were used as the utility weights in the Markov model, were available at years 1 and 3 after transplant. The utility weights of both-graft functioning for SPK recipients and kidney graft functioning for KTA recipients were corrected for selection bias as described later. For the above health states, the utilities at year 2 were estimated by an average of years 1 and 3, and the utilities at year 3 were applied throughout the remaining cycles.

For the SPK recipients with either pancreas or kidney graft failure or failure of both grafts, utilities were estimated from the available literature due to the small number of study patients in Gross et al. for these health states. These utility weights were used in every cycle for the corresponding health states. The utility assigned to the death state was equal to zero.

Table 4.4 Data sources for utilities

Health states	Data sources
KTA	
Surviving with K function	Gross et al (in press)[1]
Surviving with K nonfunction	Estimated
SPK	
Surviving with P function and K function	Gross et al (in press)[1]
Surviving with P nonfunction and K function	Estimated
Surviving with P function and K nonfunction	Estimated
Surviving with P nonfunction and K nonfunction	Estimated

[1] Preliminary report published in 1995; three-year post-transplant follow-up was completed in 1997.

Transformation of SF-36 into Quality of Well Being (QWB) Score (Fryback et al., 1997)

$$\begin{aligned}\text{QWB} = {} & 0.59196 + 0.0012588{*}\text{Physical Functioning} - 0.0011709{*}\text{Mental Health} \\ & - 0.0014261{*}\text{Bodily Pain} + 0.00000705{*}\text{General Health}{*}\text{Role Physical} \\ & + 0.0000114{*}\text{Physical Functioning}{*}\text{Bodily Pain} \\ & + 0.00001931{*}\text{Mental Health}{*}\text{Bodily Pain}\end{aligned}$$

B. A longitudinal study of QOL (Gross et al., in press)

Gross et al. (in press) followed over 300 persons with type I diabetes and ESRD seeking transplant for approximately 5 years. Sixty-five SPK and 87 KTA recipients received first-time transplant surgery between September 1990-September 1993 at the University of Minnesota Hospital. Self-administered questionnaires were completed by these study patients at pre-transplant evaluation, one-year and three-year post-transplant time periods. At pre-transplant baseline, a Diabetes Severity Index was obtained by a nurse investigator at the Diabetes Clinic. Almost all patients provided the baseline data within 1 year (mean $\pm$ SD = 4.6 $\pm$ 3.5 months) prior to transplantation. Patients receiving any retransplantation during the study period were excluded from the analyses.

As previously stated, no data from randomized, controlled trials are available for the derivation of HRQOL-based utilities in SPK and KTA recipients. Gross et al. (in press)'s study provides a unique opportunity for the comparison of utility weights between successful SPK and successful KTA. Primarily, the data on baseline patient characteristics that can be used for adjustment of the underlying differences with respect to utility and for an explanation of patients' choices on transplantation in selectivity-corrected models are available. Secondly, the original QOL study was conducted in a relatively large sample. Thirdly, multiple measurements over three years of the follow-up can detect a meaningful difference in the utility between short term and long term. Complications due to SPK are relatively more frequent within the first year after the transplant (Holohan, 1995).

Measurements

The selectivity-corrected model of utility estimation included certain variables measured by the following composite scales from Gross et al. (in press)'s study.

1. Health Status Survey Short Form 36 items (SF-36) (Ware et al., 1992). The SF-36 is a generic health status measure that assesses eight areas of HRQOL relevant to people with chronic diseases: emotional well-being (MH), social function (SF), role limitations due to emotional problems (RE), energy/fatigue (VT), pain (BP), role limitations due to physical health problems (RP), physical functioning (PF), and general health perceptions (GH).

2. Diabetes Severity Index (DSI) This measure was modified from a chart abstract protocol form (Reiber, 1988). The assessment includes questions about the secondary complications of diabetes, scored by the nurse investigator and based on physical examination, and chart abstraction at pre-transplant evaluation. Individual severity ratings are obtained for five dimensions: metabolic, vision, renal, vascular and neurologic complications. Results are combined to provide an overall rating of the severity of the chronic complications of diabetes. The original DSI was a prediction of mortality.

3. Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). This measure consists of 20 questions designed to determine the frequency within the previous week with which participants experienced depressive symptoms such as depressed mood, loss of appetite, and feelings of hopelessness.

4. Karnofsky Performance Status Scale (Grieco, 1984). This measure is widely used as the brief index of patient functioning in day-to-day activity. The self-report version was used, and the score ranged from 30 to 100. The higher the score, the better the physical functioning. For example, 100=the patient can perform normal activities without complaints, 90=the patient is able to perform normal activities but has minor complaints, 60=the patient is mostly able to perform self-care but needs occasional assistance, 40=the patient is disabled and requires special care and assistance, and 30=worse off than any of these status.

C. Mathematical approach for selectivity bias problem

The study assumed that an individual would seek SPK when he or she crossed some internal threshold of the combination of factors affecting transplant choice. The model for transplant choices can be derived as $I_i^* = Z_i\gamma + \varepsilon_i$, where Z_i is a set of the determinants of transplant choice, and ε_i is the unexplained variation in I_i^*. I_i is a dummy variable representing the transplant choice: $I_i = 1$ for SPK, $I_i = 0$ for KTA. Patient i chose SPK ($I = 1$) if $I^* > 0$, and chose KTA ($I = 0$) if $I^* \leq 0$. In other words, $I = 1$ if and only if $\varepsilon_i > -Z_i\gamma$ and $I = 0$ if and only if $\varepsilon_i \leq -Z_i\gamma$.

In a typical utility equation $Y_i = \alpha I_i + X_i\beta + u_i$, where Y_i is the QWB utility outcome, X_i is a set of covariates, and u_i is the unexplained variation in Y_i. If u_i and ε_i are correlated, then $E(u_i) \neq 0$. In this case, selection bias exists in an estimation of the treatment effect of SPK vs. KTA (α). A special statistical approach dealing with selectivity bias is used in order to correct the violation of the classical linear regression assumption when the expected value of error term is not zero (Barnow et al., 1980).

Assuming the normal distribution of ε_i, $E(\varepsilon_i | \varepsilon_i > -Z_i\gamma) = \frac{\phi_i}{\Phi_i}$ or inverse Mills ratio (λ_i), where ϕ_i and Φ_i are the probability density function and the cumulative distribution function of the standard normal variable ε_i evaluated at $Z_i\gamma$.

The selectivity-corrected model (using LIMDEP version 7.0) is based on Heckman's two step method as follows.

Step 1. Use a probit model for I to estimate γ. For each observation, compute

$$\lambda_i = \frac{f(-Z_i\gamma)}{1-F(-Z_i\gamma)} = \frac{f(Z\gamma)}{F(Z\gamma)} \text{ where } I^* > 0, \text{ and } \lambda_i = \frac{-f(-Z_i\gamma)}{F(-Z_i\gamma)} = \frac{-f(Z\gamma)}{1-F(Z\gamma)} \text{ where } I^* \leq 0,$$

based on the probit coefficients.

Step 2. Linearly regress Y on X, I and λ to estimate β, α and ρ where ρ represents correlation between u_i and ε_i.

According to the nature of the observed data (0 and 1 for transplant choice: SPK vs. KTA), and the structure of the probit model, σ_ε cannot be estimated. Therefore, the estimated γ coefficients are really $\gamma / \sigma_\varepsilon$.

Then, $E(Y_i, X_i)$ in selectivity-corrected model = $\beta X_i + \alpha I_i + \theta\lambda_i + v_i$ whereas α reflects selectivity-corrected effect of SPK over KTA and $\theta = \rho\sigma_u$. The significance of θ indicates whether the selection bias in the study sample exists or not. In this model, the effect of SPK is constrained to be an intercept shift.

This study compares the effects of SPK and KTA on utility under the assumption that everyone in the reference population receives either SPK or KTA. The sample sizes in the SPK and KTA subsamples were too small to support separate estimates for each of the two sectors.

Prediction of the utility based on the whole sample model is calculated from

$$E(Y) = E(Y\,|_{SPK})P(SPK) + E(Y\,|_{KTA})P(KTA)$$

$$E(Y) = \left\{X\beta + \alpha + \theta\left[\frac{-f(Z\gamma)}{F(Z\gamma)}\right]\right\}F(Z\gamma) + \left\{X\beta + \theta\left[\frac{f(Z\gamma)}{1 - F(Z\gamma)}\right]\right\}[1 - F(Z\gamma)]$$

$$E(Y) = X\beta + \alpha F(Z\gamma)$$

If everyone received SPK (i.e., $F(Z\gamma) = 1$), the predicted effect of SPK on QWB utility is equal to $E(Y) = X\beta + \alpha$. Similarly, the predicted effect of KTA on QWB utility is equal to $E(Y) = X\beta$ based upon the whole sample model. These estimates were used to predict the utility for the reference population. The mean values of these reference-predicted utilities are assigned to the graft functioning health states for KTA and SPK.

D. Variables in the transplant choice model and utility estimation model

According to the transplant choice and utility models hypothesized and described in Chapter 3, the list of variables in the models are summarized in Table 4.5.

The transplant choice model included degree of agreement that blood sugar is well-controlled, satisfaction with current health treatment, satisfaction with personal relationships, marital status, depression score, ability to work for pay, college education, having private health insurance, Diabetes Severity Index, and patient age. The utility estimation model includes transplant received, patient age and gender, Diabetes Severity Index, college education, and Karnofsky Performance Index. All the variables were the values at baseline. Age and diabetes severity were overlapped explanatory variables in both models.

Table 4.5 Variables in selectivity-corrected models

Variable	Measure	Response description
Satisfaction with diabetes treatment/lifestyle	How much do you agree with the following statement: "My blood sugars are well controlled." How satisfied are you with you current health treatment?	1=strongly agree, 5=strongly disagree 1=very dissatisfied, 5=very satisfied
Satisfaction with personal relationships	How satisfied are you with your personal relationships? Current marital status	1=very dissatisfied, 5=very satisfied 1=not stay married, 2=stay married
Enthusiasm in life	CES-D scale	0-60: The lower, the less depressed
Financial status	Are you now able to work for pay? College education Private health insurance covers payment for your health care expenses	1=no, 2=yes 1=no, 2=yes 0=no, 1=yes
Disease severity	Diabetes Severity Index	0-100: The higher, the more severe
Demographics	Age Gender	age of patient at transplant 1=male, 0=female
Baseline physical health	Karnofsky Performance Index	30-100: The higher the better

VI. Reference Case Analysis and Sensitivity Analysis

The reference case analysis is based on the reference population who are the beneficiaries in Medicare ESRD kidney transplant program. The reference population consists of patients age 18 and older who were recipients for primary cadaveric kidney transplant (as either KTA or SPK) and had type I diabetes as a cause of renal failure during January 1,1988 to December 31, 1998. The discount rate of 3% per year is adjusted for future costs and effectiveness for the reference case analysis (i.e., costs and utilities).

After calculating results for the reference case analysis, univariate sensitivity analyses were performed to test the effects of the model on different but plausible pancreas graft failure rates, costs for the ratio of organ acquisition, costs for the use of intensive insulin therapy instead of conventional therapy, and utilities based on a general kidney transplant population from widely cited literature. Univariate sensitivity analyses were also conducted by changing the discount rates from 3% to 5%. The reference case assumed that SPK as compared to KTA does not provide benefits for the prevention or the delay of secondary diabetes complications. If SPK did, KTA recipients would have increasing follow-up costs, along with decreasing utilities over time, due to the progression of diabetes complications.

VII. Statistical analysis

Patient characteristics at baseline were tested for the significant differences between SPK and KTA by appropriate tests. The differences in means, proportions, and distributions of non-normally distributed continuous variables were assessed by t-tests, Chi-square tests, and Mann-Whitney U tests, respectively. Cox proportional hazards regression models were used to obtain estimates for adjusted rates of patient death and graft failure after transplantation of SPK and KTA. For the two health states: SPK with both pancreas and kidney graft functioning and KTA with graft functioning, the trends in annual total costs during post-transplant period were compared using the adjusted means that were derived from generalized linear model (GLM) with gamma-distribution log-link function (Blough et al., 1999). The differences in QWB utility weights between SPK recipients with both graft functioning and KTA recipients with kidney graft functioning were detected by using regression analysis with the selectivity-corrected model. The regression model was examined for any violations in the required assumption. All statistical analyses were performed by Stata version 6.0 (College Station, TX).

VIII. Limitations

Generalizability is enhanced by the use of national-level data for most parameters. However, the exception involves the use of primary data for the utilities of certain health states. There are not comparable and reliable national-level data for the utility parameters.

With respect to data quality, the utility weights assigned to the health states of graft functioning were derived from a non-randomized study. This CEA used statistical adjustment to control for the non-random nature of the transplant allocation. Survival rates used for the derivation of transition probabilities were adjusted for only demographic characteristics, but not adjusted for diabetes severity and other risk factors. Retransplantation choice is not considered as a defined health state in the Markov models even though retransplantation is not uncommon.

For the limitations due to incompleteness of the data, cost components in this CEA did not include direct non-health care costs and pre-transplant evaluation costs. Data on the long-term follow-up costs and the utility during post-transplant time period were available for a limited time period. Gross et al. (in press)'s study, the primary data source for the utility weights, is the only available study that has longest time period of the follow-up. The predicted QWB scores for a longer time period are available from cross-sectional studies that cannot be corrected for selection bias (Matas et al., 1998).

CHAPTER 5

RESULTS

This chapter consists of five main sections. The first section describes demographic characteristics of the study patients in the two transplant groups: SPK and KTA. Transitional probabilities for each health state are provided in the second section. The third section describes transplant surgery costs and annual follow-up costs obtained by using a gamma distribution with log link function. The fourth section reports estimates of utilities obtained from the selectivity-corrected model and from published literature. The results of cost-effectiveness analysis and sensitivity analysis are presented in the fifth section.

I. Patient Characteristics

A. SPK recipients enrolled in Medicare ESRD Program

As previously addressed, patient and graft survival analyses and estimation of costs for health states in SPK are based on recipients who were enrolled in the Medicare ESRD program. Comparison of the patient characteristics at the time of SPK transplant surgery between those who were Medicare beneficiaries (N=3,700) and those who were not (N=2,911) is presented in Table 5.1. This analysis is done for the patients who received primary transplant during January 1988 to December 1998. Fifty-six percent of the beneficiaries were enrolled in the Medicare ESRD program. Although there are differences in age at transplant, in age when type I diabetes was diagnosed, and in transplant waiting time are statistically significant, the magnitudes of these differences are relatively small. Case-mix variations in gender and race are very similar.

Table 5.1 Demographic characteristics and selected outcomes of SPK recipients enrolled and not enrolled in Medicare ESRD Program

	SPK recipients and Medicare ESRD Program		P value*
	Medicare (N=3,700)	Non-Medicare (N=2,911)	
Age at transplant (years)			
Mean (SD)	37.0 (7.2)	37.4 (7.6)	p=0.0354
Gender (%)			
Male	59.2	59.2	
Race (%)			
White	91.6	90.2	
Black	7.5	8.6	
Other	0.8	1.1	
Age at type I diabetes diagnosis (years)	N=1330	N=1994	
Mean (SD)	14.5 (0.2)	13.0 (0.2)	p<0.0001
Waiting time (days)			
Mean (SD)	240.2 (250.7)	226.7 (237.0)	p=0.0409
Length of hospital stay (days)**			
- Mean (SD) for all-year transplant	22.4 (49.9)	22.4 (31.8)	
- Mean, median for transplant year:			
1988	28.7, 20.0	31.6, 23.0	
1989	48.3, 21.0	28.9, 23.0	
1990	25.1, 19.0	25.4, 19.0	
1991	23.2, 18.0	25.3, 19.5	
1992	25.7, 20.0	24.4, 19.0	
1993	24.5, 18.0	28.0, 20.0	
1994	22.8, 16.0	21.2, 16.0	
1995	19.7, 15.0	18.0, 14.0	
1996	19.6, 14.0	20.8, 12.0	
1997	17.0, 11.0	16.4, 11.0	
1998	17.0, 11.0	15.6, 10.0	
Patient survival rate after transplant (%)			
Year 1	93.0	92.6	
Year 2	90.6	90.2	
Year 3	88.3	88.1	
Pancreas graft survival rate after transplant (%)			p<0.0001
Year 1	83.5	79.4	
Year 2	80.0	76.5	
Year 3	77.0	73.2	
Kidney graft survival rate after transplant (%)			p<0.0001
Year 1	88.8	83.7	
Year 2	86.0	79.1	
Year 3	82.8	74.9	

* Only P values less than 0.20 are reported

** From UNOS pancreas database

Lengths of hospital stay for transplant surgery between the Medicare and non-Medicare groups are similar and declined substantially over time. Sub-group analysis of those who had transplant performed during January 1 to December 31, 1998 shows the median lengths of hospital stay are 11.0 and 10.0 days in the Medicare and non-Medicare groups, respectively.

Data on patient and graft survivals in the SPK non-Medicare group are complete during the first three years following transplantation. Patient survival rates between the two groups are comparable in every year (93, 90, and 88% at years 1, 2, and 3, respectively). However, graft survivals to 3 years after transplant in the Medicare beneficiaries are higher than in the non-Medicare group (4% for pancreas graft, 5-8% for kidney graft) when the allograft failures are defined as graft failure (i.e, return to dialysis or insulin therapy), or death.

In sum, SPK recipients who were included in this study seem to have a relatively better outcome in terms of graft survivals than those excluded.

B. SPK recipients vs. KTA recipients in the study sample

The reference population for this study consists of 12,593 Medicare beneficiaries who had type I diabetes as a cause of renal failure. The patients received either primary KTA or primary SPK from cadaveric organ donors during January 1988 to December 1998. Average age of this population is 42.0 years and 59% are male. Majority of the reference population are white (79%), and 12% are black.

Baseline characteristics available for a comparison between SPK and KTA recipients are demographic characteristics (Table 5.2). Among the patients eligible for this study, the majority of the patients are white and nearly 60% are male. KTA patients are older, on average, than SPK recipients (44 vs. 38 years). Eighty-two percent of SPK patients are 25-44 years of age whereas 55% of KTA patients are in this age range. Fortyone percent of KTA patients are in the age range of 45-64 years. Among the 3,700 SPK recipients, 87% are white and 7% are black. Among the 8,893 KTA recipients, 76% are white and 15% are black. The demographic differences between SPK and KTA indicate the need of an adjustment for case-mix variation.

Table 5.2 Demographic characteristics of SPK and KTA recipients in the reference population (N=12,593)

	SPK (N=3,700)	KTA (N=8,893)	Reference Population (N=12,593)	P value between SPK vs. KTA
Age (years)				
Mean (SD)	37.5 (0.1)	43.9 (0.1)	42	p<0.0001
Age category (%)				p<0.0001
18-24 years	2.3	1.7		
25-34 years	37.5	22.4		
35-44 years	44.6	32.4		
45-54 years	14.4	25.2		
55-64 years	1.1	15.7		
65 years and over	0.0	2.7		
Gender:				
Male (%)	59.2	59.3	59	p=0.0129
Race				
White (%)	87.4	76.0	79.0	p<0.0001
Black (%)	7.1	14.6	12.0	
Other (%)	5.5	9.3	9.0	

II. Comparison of Patient and Kidney Graft Survivals between SPK and KTA

Since there has been dramatic improvement in immunosuppressive therapy since 1994, comparisons in patient and graft survivals between the SPK and KTA were done separately for the transplant surgery performed during 1994 to 1998 and transplants performed during 1988 to 1993. The maximum time of the full-year follow-up for patients who received transplants during 1994-1998 (N=7,120) is 4 years (median = 2.8 years). In this subgroup, the first-year survival rates are 95.9% for KTA and 94.6% for SPK (Table 5.3). By year 4 after transplant, approximately 87% of the patients in each transplant group were still alive. Among those who received transplant during 1988-1993 (N=5,473), the first-year survival rates are 94.3% for KTA and 92.0% for SPK and approximately 83% in each of the two groups survived through 4 years following transplant.

Table 5.3. Adjusted patient survivals* to 4 years after transplant for the reference population (N=12,593)

Years after transplant	Transplant year			
	1994 – 1998		1988 – 1993	
	KTA (N=4,657)	SPK (N=2,463)	KTA (N=4,236)	SPK (N=1,237)
1	0.959	0.946	0.943	0.920
2	0.934	0.924	0.911	0.886
3	0.906	0.904	0.873	0.857
4	0.871	0.868	0.830	0.836

* Rates adjusted by gender, race, and age using Cox baseline hazards for male, white, and age at 35 years

In the old era of transplant, patient survivals in the first three years following SPK are worse than those in KTA. In the new era, the survival for SPK and KTA recipients improved and the survivals between the two groups became similar. Based on a Cox proportional hazards model, the differences in patient survivals between the two transplant groups (SPK vs. KTS) are not statistically significant (P=0.694) for the transplants performed during 1994-1998.

Seventy-eight percent of the 5,473 patients who received transplant during 1988-1993 were alive beyond the fourth year after transplantation with the median follow-up time of 7.2 years. For SPK recipients surviving at least 4 years, there is 42% reduction in the rate of death as compared to those of KTA, in the multivariate Cox proportional hazards model (Table 5.4). Ethnicity (black) seems to be an significant predictor for mortality as well, but does not reach statistical significance. Age significantly predicts the death rate.

Table 5.4 Death rate ratio for patients receiving transplants during 1988-1993 and surviving for a minimum of 4 years after transplant (N=4,245)

	Hazard rate ratio	95% confidence interval	P value
SPK	0.58	0.48 – 0.69	0.0000
Age	1.04	1.03 - 1.05	0.0000
Female	1.05	0.93 - 1.18	0.4650
Black	1.16	0.97 - 1.39	0.1070
Other	0.91	0.71 - 1.15	0.4140

Table 5.5 shows patient survival adjusted for age, gender, and race for those who received transplants during 1988-1993 and survived through 4 years after the transplantation. The difference in patient survivals between SPK and KTA is apparent in every year. At year 11 following transplantation in this time period, 74% of SPK patients are still alive, compared to 54% of KTA patients.

Table 5.5 Adjusted patient survivals* to 11 years after transplant for those who received transplant during 1988-1993 and survived through 4 years after transplant

Years after transplant	Transplant year 1988 – 1993	
	KTA (N=3,283)	SPK (N=1,018)
5	0.949	0.967
6	0.894	0.939
7	0.825	0.906
8	0.764	0.865
9	0.709	0.792
10	0.630	0.754
11	0.543	0.740

* Rates adjusted by gender, race, and age using Cox baseline hazards for male, white, and age at 35 years

We found a similar pattern in the relationship between transplant group and kidney graft survival when the kidney graft failure is defined as graft failure or death. In the more recent era of transplantation (1994-1998), kidney graft survival rates of SPK patients are 89, 85, 81, and 77% in years 1, 2, 3, and 4 after transplant and those of KTA are 91, 87, 83, and 79%, respectively. The differences in kidney graft failure rates between the two transplant groups are not statistically significant (P=0.207) within the first four years after transplantation.

Table 5.6 presents the hazard rate ratio for the patients who received the transplant during 1988-1993 and had their kidney graft functioned through the fourth year after the transplant (N=3,837), with median follow-up of 7.10 years. The result shows that SPK reduces the rate of the kidney graft failure by 36% as compared to KTA. Age and being black are significant predictors of the graft failure.

Table 5.6 Failure rate ratio of kidney graft for patients receiving transplants during 1988-1993 whose kidney graft functioned for a minimum of 4 years after transplant (N=3,837)

	Hazard rate ratio	95% confidence interval	P value
SPK	0.64	0.54 – 0.75	<0.0001
Age	1.02	1.02 – 1.03	<0.0001
Female	1.07	0.95 – 1.21	0.247
Black	1.41	1.17 – 1.70	<0.0001
Other	1.11	0.88 – 1.40	0.380

The difference in kidney graft survivals between SPK and KTA is presented in Table 5.7. At year 11 following the transplantation of this subgroup, 66% of SPK patients had kidney graft functioning, compared to 49% of KTA. The SPK group has better kidney graft survival than the KTA group in every follow-up year in time period.

Table 5.7 Adjusted kidney graft survivals* to 11 years after transplant for those who received transplant during 1988-1993 and their graft survived through 4 years after transplant

Years after transplant	Transplant year 1988 – 1993	
	KTA (N=2,909)	SPK (N=928)
5	0.936	0.953
6	0.868	0.913
7	0.792	0.863
8	0.726	0.800
9	0.659	0.760
10	0.578	0.732
11	0.490	0.664

* Rates adjusted by gender, race, and age using Cox baseline hazards for male, white, and age at 35 years

Tested for nonlinear relationship between patient survival and age using quadratic terms in all Cox proportional hazards models, no interaction was detected. Similar non-significant results were obtained for interactions between age and transplant choice. The proportionality assumption underlying Cox proportional hazards regression was tested for all models. Ln[-Ln{S(t)}] curves were examined to affirm that the survival functions of the two groups remained parallel over time.

III. Transitional Probabilities Assigned to Health States in a Markov Model

A Markov model was constructed to allow comparison between the two transplant options for life expectancy, life-time costs and QALYs. This approach allows the simultaneous and quantitative consideration of costs and effectiveness including survival and quality of life. The Markov decision analysis was done in hypothetical patients based on characteristics of the reference population who had type I diabetes as a cause of renal failure.

In the Markov model, patients move from one health state to another on the basis of transitional probabilities determined from transplant databases as described in Chapter 4. The average survivals of patients and grafts conditional on a given health state predicted from the reference population were used in the Markov model. The average number of the survived cohorts over the total number of simulated cycles yields years of life expected for each transplant group. As patients cycle through the model, they accumulate costs and utilities measured as QALY until all the cohorts move into the death or absorbed state.

Table 5.8 presents transitional probabilities for two health states based on graft status of KTA recipients. In the first year after transplantation for patients who had a successful graft, probability of kidney graft failure is 0.10, which is the highest rate during the 10 years of available follow-up period. The graft failure rate decreases to about 2-3% during 2-4 years following the transplantation, then rises again from 4 % in year 5 to almost 7% in year 10. Probability of transition to death in the health state of kidney graft functioning is 0.02 in the first year and increases gradually to 0.11 in the last year of observation. Death rate in the KTA recipients who had graft failure is much greater than their graft functioning counterparts in every follow-up year. Probability to death in the health state of kidney graft failure (0.39) is highest in the first year after the failure of the kidney graft and is in the range of 0.09-0.26 thereafter.

Table 5.8 Probabilities of transition between health states for KTA

Year after transplant or Year after graft failure	From KTA graft functioning			From KTA graft failure	
	Recursive	To death	To graft failure	Recursive	To death
1	0.8820	0.0205	0.0975	0.6104	0.3896
2	0.9418	0.0279	0.0303	0.8943	0.1057
3	0.9454	0.0322	0.0224	0.9078	0.0922
4	0.9380	0.0389	0.0231	0.8302	0.1698
5	0.9124	0.0494	0.0382	0.8047	0.1953
6	0.9007	0.0566	0.0427	0.7459	0.2541
7	0.8789	0.0772	0.0439	0.8092	0.1908
8	0.8862	0.0684	0.0454	0.7799	0.2201
9	0.8699	0.0770	0.0531	N/A	N/A
10	0.8250	0.1094	0.0656	-	N/A

N/A = Not available due to N < 30

Notably, the transitional probabilities for the two health states of KTA increase in the last year of available observation. Probabilities for the remaining yearly cycle in each of the two health states are assumed to be equal to the probabilities of the last available year.

Two separate tables present probabilities of the transition between health states in SPK recipients. Table 5.9A presents two health states for pancreas and kidney grafts: either functioning or failure. Table 5.9B presents health states with the status of functioning graft of either pancreas or kidney.

Table 5.9A Probabilities of transition between health states for SPK

Year after transplant or Year after graft failure	From SPK P and K graft functioning*				From SPK P and K graft failure	
	Recursive	To death	To K graft failure	To P graft failure	Recursive	To death
1	0.7735	0.0230	0.0921	0.1114	0.3474	0.6526
2	0.9325	0.0152	0.0314	0.0209	0.7685	0.2315
3	0.9337	0.0163	0.0329	0.0171	0.7952	0.2048
4	0.9373	0.0194	0.0353	0.0080	0.9065	0.0935
5	0.9316	0.0205	0.0270	0.0209	-	N/A
6	0.9379	0.0176	0.0297	0.0148	-	N/A
7	0.9129	0.0238	0.0377	0.0256	-	N/A
8	0.9220	0.0304	0.0398	0.0078	-	N/A
9	-	0.0604	0.0230	N/A	-	N/A
10	-	N/A	0.0632	N/A	-	N/A

* There were no events of failures of P and K grafts occurring at the same time
N/A = Not available due to N < 30 and loss to follow-up of P graft failure events

The failure rate of the pancreas graft is about 11% in the first year following successful SPK, then decreases markedly to about 1-2% until the eighth year. Transition to kidney graft failure from the successful SPK health state shows a similar pattern over time. The kidney graft failure rate is highest in the first year (about 9%) and decreases to 2-4% thereafter through the ninth year. The failure rate, however, increases to 6% in year 10.

Probability of death after successful SPK is relatively stable about 0.02-0.03 for the first eight years, then increases to 0.06 at year 9. As anticipated, SPK recipients who had both pancreas and kidney graft failures are more likely to die than those with functioning grafts. The highest probabilities of death occurs in the first year after graft failure with a death rate of 65%. The death rate decreases dramatically to 23-20% during the following two years and then falls to 9% in the fourth year.

Table 5.9B Probabilities of transition between health states for SPK

Year after transplant or Year after graft failure	From SPK P graft functioning and K graft failure			From SPK K graft functioning and P graft failure		
	Recursive	To death	To P and K graft failure	Recursive	To death	To P and K graft failure
1	0.3967	0.3709	0.2324	0.7230	0.0689	0.2081
2	0.8722	0.1044	0.0234	0.9124	0.0196	0.0680
3	-	0.1377	N/A	0.9250	0.0282	0.0468
4	-	N/A	N/A	0.7982	0.1288	0.0730
5	-	N/A	N/A	0.8206	0.0770	0.1024
6	-	N/A	N/A	0.8656	0.0800	0.0544
7	-	N/A	N/A	0.7791	0.1780	0.0429
8	-	N/A	N/A	-	N/A	N/A
9	-	N/A	N/A	-	N/A	N/A
10	-	N/A	N/A	-	N/A	N/A

N/A = Not available due to N < 30 and loss to follow-up of P graft failure events

Transitions from the SPK health states with a functioning graft of either pancreas or kidney to the health states of second graft failure show a similar pattern over time (Table 5.9B). Failure rate of the second graft is highest in the first year after failure of the first graft (23% for pancreas and 21% for kidney) and decrease considerably thereafter to an average of 2.3% for pancreas and of 6.5% for kidney. Transitional probability to death after kidney graft failure in SPK recipients is highest (37%) in the first year and decreases thereafter to an average of 12.1%. The death rate after pancreas graft failure shows a different pattern, where the first year death rate of 7% is less than an average of 8.5% across the six following years.

For the remaining yearly cycles for the SPK health states with both grafts functioning, probabilities of the transitions to kidney graft failure and to death are assumed to be equal to the probabilities in the last available year. Probability of the transition to pancreas graft failure is set as an average of the probabilities from the second to the eighth years, because the year to year variation is high.

Typically an SPK patient who has pancreas and kidney graft failures needs insulin therapy and dialysis so does a KTA patient whose kidney graft has failed. These two health states can be considered equivalent in health status. Therefore, probabilities to death for the KTA graft failure health state were used for filling the missing data in year 5 and thereafter on the transitional probabilities for SPK with failure of both grafts.

An SPK patient who has only pancreas graft failure and a KTA patient with graft functioning are considered to be in the similar health status. The unavailable probabilities in year 8 and thereafter of the transitions to both graft failures and to death in the SPK health state with only pancreas graft failure were assumed to be equal to the corresponding transitional probabilities from the KTA graft functioning health state.

IV. Cost Estimates

Distribution of health care utilization including observed transplant surgery costs, length of hospital stay for transplant surgery, and observed annual costs of each follow-up year for each health state is found positively skewed as anticipated. Therefore, these values were examined for the exact relationship between variance and mean in order that a suitable modeling for estimation can be performed (Manning, 1998; Blough et al., 1999). This study reports predicted mean values based on generalized linear models that account for the distribution patterns.

A. *Costs of hospitalization for transplant surgery*

Table 5.10 presents the mean values of predicted costs and length of hospital stay for transplant surgery by transplant year of KTA and SPK based on Medicare claims data. The hospitalization costs reported in the table do not include payments for organ acquisition and professional fees. The model covariates include transplant procedure (KTA *vs* SPK), age, gender, race, and transplant years. For transplant surgery cost data, the variance is approximately the cubic of mean value. Hence, the inverse Gaussian distribution is assumed. The variance of length of stay is about the square of mean and the gamma distribution with log link function is used for the prediction model.

Table 5.10 Mean predicted cost and length of hospital stay for transplant surgery by transplant year

Transplant year	KTA			SPK		
	N	Cost (1998 US$)	LOS (days)	N	Cost (1998 US$)	LOS (days)
1991	426	30,085.22	13.9	82	64,597.39	22.3
1992	297	31,192.91	15.0	71	66,983.49	23.9
1993	475	30,152.96	13.6	126	64,682.89	21.8
1994	500	30,243.92	13.4	170	64,535.58	21.3
1995	498	29,461.76	11.2	180	63,090.19	17.9
1996	557	28,719.16	10.1	195	61,513.91	16.1
1997	524	27,400.35	9.8	125	58,458.12	15.5
1998	224	25,942.71	9.5	52	55,458.46	15.2

In KTA transplant procedure, the hospitalization costs for transplant surgery decline over time, so does the length of hospital stay. This finding is consistent with the review by Evans (1998). In the SPK group, both costs and length of stay also decline over time. There is a sizable difference in the costs of hospitalization for transplant surgery between the two procedures. Hospitalization costs are higher in SPK than in KTA for every transplant year.

Two other elements of transplant costs are, then, added to the cost of hospital stay for transplant surgery to complete the total transplant-related costs. Since organ acquisition costs are allocated to non-ESRD beneficiaries on a 'pass through' basis and cannot be calculated directly from an individual claims record, this study used the average kidney acquisition payment of $28,699.75 for KTA. The acquisition payment for pancreas and kidney in SPK was $44,398.51. In addition, Medicare claims data used in this study did not include professional fees for transplant surgery associated with additional pancreas transplant of an SPK procedure. This study used $2,300 for fees associated with the surgeon and anesthesiologist. Justification of the amount of organ acquisition costs and professional fees has already been described in Chapter 4.

B. Annual total costs

Annual total cost data reported here include those related and unrelated to SPK and KTA. Table 5.11 summarizes the predicted means of annual total costs occurring in each health state over time. Only full-year data on costs were counted. Data with observations less than thirty patients were not presented and not used in this study. KTA with graft functioning health state contributed the cost data for 10 years with the largest sample sizes, followed by 7 years of KTA with graft failure and SPK with both graft functioning health states. Data were available for only 3 years for SPK with both grafts failure.

Table 5.11 Mean predicted annual costs by health state in each year following transplantation

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
KTA: K function	N=3,253	N=4,365	N=3,786	N=2,740	N=1,709	N=1,132	N=710	N=369	N=155	N=51
Mean	97,686.63	18,547.27	16,280.75	15,764.27	18,758.55	16,642.87	15,783.40	16,927.60	16,780.65	19,795.16
KTA: K failed	N=736	N=574	N=423	N=222	N=122	N=62	N=31	N/A	N/A	N/A
Mean	81,542.59	59,559.54	54,872.76	62,109.32	67,177.69	49,383.68	45,975.30			
SPK: P and K function	N=938	N=1,347	N=1,101	N=656	N=332	N=214	N=111	N/A	N/A	N/A
Mean	172,435.75	24,115.63	18,117.51	13,825.91	17,400.44	16,274.95	12,613.92			
SPK: P failed, K function	N=177	N=171	N=132	N=80	N=45					
Mean	76,069.36	23,933.70	24,220.18	18,522.12	19,336.99					
SPK: P function, K failed	N=147	N=103	N=37	N/A	N/A					
Mean	62,423.36	29,755.45	40,377.08							
SPK: P and K failed	N=75	N=58	N=42	N/A	N/A					
Mean	94,638.35	57,171.45	58,943.82							

N/A = Not available due to N < 30

This study found that the variance of annual total costs conditional on health state, age, gender, race, and year of the beginning of health state was about the square of mean value for almost every year. Hence, the estimation of annual costs assigned into the Markov model is based on generalized linear model that uses gamma distribution with log-link function. The mean predicted costs for every health state in each year following transplantation are presented in Table 5.12, and these values were then used in the Markov model. These predicted costs were based on age, gender, and race characteristics of the 12,593 reference population and represent the health care technology in 1997 and 1998.

Table 5.12 Mean predicted costs by health state of the reference population

Year*	KTA graft functioning	KTA graft failure	SPK both graft functioning	SPK, pancreas graft failure	SPK, kidney graft failure	SPK both graft failure
1	97,742.33	81,690.50	176,532.86	78,072.51	65,928.80	96,345.18
2	21,118.15	65,926.91	28,225.44	27,697.67	35,065.94	64,735.31
3	14,470.08	48,376.11	17,076.29	23,186.70	39,121.40	55,140.60
4	15,150.66	55,992.42	14,298.76	19,295.58	-	-
5	18,638.95	62,362.68	17,726.94	20,870.36	-	-
6	17,290.36	45,913.10	18,359.97	-	-	-
7	17,909.25	45,376.51	16,129.22	-	-	-
8	14,673.16	-	-	-	-	-
9	18,272.20	-	-	-	-	-
10	20,014.62	-	-	-	-	-

Year after transplant for two health states: KTA graft functioning and SPK both graft functioning, or year after graft failure for other health states

The resulting predicted costs were put into each yearly cycle in Markov model. Data from Medicare claims record used in this study did not contain payments for insulin and diabetes monitoring kits. Therefore, the annual costs of $1,911.55 for conventional insulin therapy were added to the costs for KTA health states and for SPK health states with pancreas graft failure.

Results from the generalized linear model estimation for the observed annual costs in all health states reveal that costs in the recipients who had successful SPK are significantly higher than in the recipients who had successful KTA during the first three years and become non-significantly different thereafter. In the first year after transplant, total cost predicted for SPK graft functioning health state is 1.8 times higher than KTA graft functioning health state. The relatively higher costs of the SPK graft functioning health state continue during the second and third years. When insulin therapy costs are included, annual total costs for the SPK graft functioning health state are less than those for the KTA graft functioning health state during the fourth and seventh years.

Recipients who had successful KTA are similar to those with pancreas graft failed SPK in that both groups need the insulin therapy. Interestingly, cost occurring in the SPK recipient who had pancreas graft failure in the first year is relatively high. The results show that after the first year of the beginning of health states, the SPK group had higher total cost than the KTA group.

For the third pair of comparison, when compare between KTA graft failure and SPK with only kidney graft failure, the predicted costs from the KTA group are higher than the SPK group in every of the first 3 years after graft failure.

Imputation of costs to be used in the Markov model where the observed data were not available for a prediction was done according to the following assumptions. For KTA with graft functioning and graft failure health states and SPK with only pancreas graft functioning and both pancreas and kidney graft functioning health states, costs for the remaining yearly cycles were based on mean values of the costs available in year 3 and thereafter. Similar to the imputation of the transitional probabilities, costs for the unavailable years of SPK health state with pancreas graft failure were assumed equal to those of KTA functioning health state, and costs for SPK both grafts failure health state were set equivalent to those of KTA graft failure.

V. Utility

The quality weights (i.e., utilities) used for the reference case in the present study were based on the data collected from Gross et al. (in press) study for three health states: SPK with both graft functioning; KTA with kidney graft functioning; and SPK with pancreas graft failed. For other health states, the utilities were based on the work of Laupacis et al. (1996).

A. Utility for health states of KTA graft functioning and SPK both graft functioning

An individual's utility was derived originally from Gross et al.'s study by transforming observed SF-36 health profiles into predicted QWB scores. The QWB scores specific to KTA graft functioning and SPK both graft functioning health states were then corrected by using selectivity-corrected models.

Patient characteristics in Gross et al.'s study

At year one after transplant, 64 KTA and 30 SPK recipients with successful grafts responded to the study questionnaires. At year three following transplant, 33 KTA and 22 SPK recipients who continued to have graft functioning responded to the questionnaires. Table 5.13 shows selected patient characteristics measured at baseline.

Table 5.13 Sociodemographic and medical characteristics at baseline

	KTA	SPK	P values*
Year 1 samples	N=64	N=30	
Age: mean years (SD)	39.62 (10.60)	36.40 (7.73)	p=0.140
Male (%)	56.3	66.7	
College educated (%)	33.9	50.0	p=0.105
Married or live together (%)	48.4	56.7	
Current work status (%)			p=0.026
full time or part time	33.3	62.1	
not working because of health (disabled)	46.7	20.7	
student, home maker, retired, and other	20.0	17.2	
Able to work for pay (%)	36.5	66.7	p=0.008
Duration of diabetes: mean years (SD)	23.92 (8.47)	24.47 (7.19)	
Kidney involvement (%)			
on dialysis	56.5	56.7	
serum creatinine > 4 mg/dl without dialysis	27.4	30.0	
serum creatinine 1.4 - 4 mg/dl	14.5	13.3	
serum creatinine < 1.4 mg/ dl, but proteinuria > 1 mg/dl	1.6	-	
Hypertension (%)	82.5	93.3	
Amputation (%)	10.7	3.3	
Diabetic eye disease (%)			
no involvement	4.8	7.1	
retinopathy	76.2	78.6	
blind or functionally blind	19.0	14.3	
Diabetes Severity Index: mean score (SD)	41.15 (11.27)	39.29(10.52)	
ER visit during last year (%)	58.7	66.7	
Hospitalization during last year (%)	68.3	76.7	
Year 3 samples	N=33	N=22	
Age: mean years (SD)	38.85 (8.73)	35.59 (6.70)	p=0.147
Male (%)	45.5	59.1	
College educated (%)	30.3	45.5	p=0.195
Married or live together (%)	45.5	59.1	
Current work status (%)			
full time or part time	34.4	57.1	
not working because of health (disabled)	50.0	28.6	
student, home maker, retired, and other	15.6	14.3	
Able to work for pay (%)	39.4	63.6	p=0.102
Duration of diabetes: mean years (SD)	24.58 (7.83)	24.59 (7.49)	
Kidney involvement (%)			
on dialysis	50.0	54.5	
serum creatinine > 4 mg/dl without dialysis	25.0	27.3	
serum creatinine 1.4 - 4 mg/dl	25.0	18.2	
serum creatinine < 1.4 mg/ dl, but proteinuria > 1 mg/dl	-	-	
Hypertension (%)	75.0	95.5	p=0.065
Amputation (%)	10.7	4.5	
Diabetic eye disease (%)			
no involvement	6.1	4.5	
retinopathy	72.7	77.3	
blind or functionally blind	21.2	18.2	
Diabetes Severity Index: mean score (SD)	41.40 (9.94)	40.60 (9.19)	
ER visit during last year (%)	57.6	63.6	
Hospitalization during last year (%)	62.5	72.7	

* Exact P values are given if $p<0.20$

Most baseline characteristics are very similar between the two groups except distribution on ability to work for pay and working status. Baseline characteristics of the year three cohorts were similar to year one sample.

In general, the transplant recipients ranged in age from 18 to 64 years (mean=37 years), slightly more than half were male, and more than half were married. Proportions of SPK recipients who had college education and ability to work for pay at pretransplant assessment are higher than the KTA counterparts. The patients had diabetes for about 25 years. The two groups were comparable with respect to diabetic eye complications, kidney involvement and DSI scores. Approximately 18% of the candidates reported blindness of one or both eyes; about 50% were on renal dialysis; and 80-90% had hypertension. Among the other components of the DSI, vascular and neurologic impairments and metabolic disorders ($HgbA_1C$) were similar across the two groups. ER visit and hospitalization during the last year prior to transplantation were quite more common in the SPK group than the KTA, however, they were not statistically significant.

Utility estimated by selectivity-corrected model

An individual's prognosis for developing multiple complications of diabetes, that was not measured in the study could affect their decision on transplant choice and correlate with the utility outcome after transplant. This study employed a series of selectivity-corrected models controlling for such unobserved variables explaining the individual's decision on choosing transplant type. In the first step, the probability of choosing SPK versus KTA was estimated by probit model. Then the study used the linear prediction of transplant choice to calculate an inverse Mills' ratio (lambda) of being an SPK or KTA recipient. The estimated lambda was included as an additional variable in the regression equation that predicts utility outcome. At year one and year three after transplant, the transplant choice and utility outcome were modeled separately. The statistical significance and sign associated with the lambda's coefficient in the utility prediction model indicates the magnitude of selection bias that would have been present in the estimates if the lambda was not included in the utility outcome equation.

Table 5.14 reports effects of the transplant choice determinants on the likelihood in choosing SPK over KTA based on probit model.

Table 5.14 Parameter estimates from probit models: probability index for SPK (=1) vs. KTA (=0)

Explanatory variable	Year 1 model			Year 3 model		
	Parameter estimate	*t*-ratio	*P*-values	Parameter estimate	*t*-ratio	*P*-values
Age	-0.038	-1.844	0.065	-0.049	-1.611	0.107
Satisfaction with current health treatment	-0.334	-1.991	0.046	-0.380	-1.794	0.078
Satisfaction with personal relationships	-0.433	-2.620	0.009	-0.536	-2.321	0.078
Marital status	0.756	1.772	0.076	0.918	1.760	0.020
Depression score	-0.064	-2.998	0.003	-0.080	-2.628	0.078
Ability to work for pay	0.699	1.844	0.065	1.037	1.942	0.009
College education	-0.624	-1.810	0.070	-0.517	-1.132	0.052
Diabetes Severity Index	0.058	0.348	0.728	0.036	1.365	0.258
Degree of agreement in blood sugar well controlled	-0.225	-1.295	0.195	-0.064	-0.288	0.773
Having private health insurance	0.435	0.946	0.344	0.1455	0.239	0.811
Initial log-likelihood	-57.69			-36.50		
Final log-likelihood	-40.83			-26.02		
Number of patients	SPK: N=30 KTA: N=61			SPK: N=32 KTA: N=22		

Models at year 1 and year 3 yielded similar results. Most variables as hypothesized are statistically significant, and a few of them are marginally significant.

Even though three variables: degree of agreement in blood sugar well controlled, having private health insurance, and DSI do not reach significance, they were kept in the choice model as covariates in order to adjust for differences in susceptible risk, comorbidity and care accessibility. An individual who rated him/herself a high degree of agreement with blood sugar well controlled and still developed serious diabetes complication such as nephropathy as in our study patients, might be willing to seek SPK. The patients included into Gross et al.'s study did not have Medicare coverage for an additional pancreas transplant. The variable 'having private health insurance for medical care' that did not reach statistical significance was then kept in the transplant choice model in order to partly control for financial barriers to access care.

Despite a small sample size, the transplant choice was predicted quite well. The proportionate reduction in prediction error is 55% and 41% for the models at year 1 and year 3, respectively. This goodness-of-fit value is based on Del measure of prediction success (Hildebrand et al., 1977).

Contribution of explanatory variables in the choice model is largely consistent with the theoretical background described in Chapter 3. The more dissatisfied with diabetes treatment and personal relationship individuals have, the more likely they chose SPK. Those who were younger, staying married, being able to work for pay, and less depressed tended to choose SPK. College education also affected the SPK choice of the study samples.

An estimation of treatment effect on utility outcome was based on regression analysis. Table 5.15 compares selectivity-corrected models with OLS models based on the variables proposed in the theoretical background. Adjusted effect of SPK over KTA on QWB scores is reflected by regression coefficient of the indicator variable for transplant type (1=SPK, 0=KTA).

Table 5.15 Selectivity-corrected and ordinary least squares estimates for utility: whole sample

Year 1 SPK: N=30, KTA: N=61

Explanatory variable	Selectivity-corrected			Ordinary least squares		
	Parameter estimate	*t*-ratio	*P*-values	Parameter estimate	*t*-ratio	*P*-values
Intercept	0.582	5.762	0.000	0.643	6.576	<0.001
Patient age	-0.0017	-1.810	0.062	-0.0021	-2.384	0.020
Patient gender	-0.0074	-0.441	0.660	-0.0139	-0.817	0.416
Diabetes severity index	-0.0005	-0.601	0.548	-0.0004	-0.593	0.555
Karnofsky Performance Index	0.0019	2.979	0.003	0.0020	2.815	0.006
SPK group indicator	0.0674	2.053	0.040	0.0196	1.131	0.262
Lambda	-0.0393	-1.769	0.077	-	-	-
R^2		0.266			0.248	
Rho		-0.4734			-	

Year 3 SPK: N=22, KTA: N=32

Explanatory variable	Selectivity-corrected			Ordinary least squares		
	Parameter estimate	*t*-ratio	*P*-values	Parameter estimate	*t*-ratio	*P*-values
Intercept	0.733	6.028	<0.001	0.7877	6.437	<0.001
Patient age	-0.0012	-0.814	0.416	-0.0022	-1.617	0.113
Patient gender	-0.0272	-1.382	0.167	-0.0209	-0.997	0.324
Diabetes severity index	-0.0019	-1.602	0.109	-0.0018	-1.459	0.151
Karnofsky Performance Index	0.0006	0.789	0.430	0.0007	0.794	0.431
SPK group indicator	0.1067	2.623	0.009	0.0531	2.459	0.018
Lambda	-0.0462	-1.713	0.087	-	-	-
R^2		0.351			0.304	
Rho		-0.6128			-	

The selectivity-corrected estimates are two to three times larger than the uncorrected estimates. The marginal significance for lambda in both year 1 and year 3 models can be explained by the small sample size. Negative coefficients for the lambda indicated that omitted variables are positively associated with the transplant choice contribute negatively to utility outcomes (Dowd et al., 1996).

The validity of selection results depends on "identifying" variable(s) that affect SPK or KTA transplant choice but not the utility outcomes. The identifying variables in this study include the marital status and college education at pre-transplant assessment. To test for no-correlation between the excluded variables explaining transplant choice but not the utility outcomes, marital status and college education in the choice model were added into the outcome equation. Mutual contribution of the two variables in this augmented regression was not statistically significant ($F_{(2,74)}$=0.21 for year 1; $F_{(2,45)}$=0.30 for year 3).

Results from the selectivity-corrected models indicate that SPK recipients with both graft functioning have expected utilities higher than KTA recipients with graft functioning in both year 1 and year 3 after transplantation. For those with successful graft functioning, SPK yielded short-term utilities measured at year one higher than KTA. A successful pancreas graft is estimated to add 0.067 point of QWB scores to a kidney transplant. For long-term utilities measured at year three after transplant, SPK recipients had QWB scores 0.11 point higher than KTA recipients.

Regression diagnostics and specification tests for the final models did not show violations in the required assumptions for classical linear regression analysis. These included detection of problems with regard to outliers (Cook, 1977), non-normality of residuals (Shapiro and Wilk, 1965; D'Agostino et al., 1990), non-linearity (Pregibon, 1979), and heteroskedasticity (Park, 1966; Glejser, 1969; Cook and Weisberg, 1983). Ramsey RESET test (1969) based on a regression of QWB on the originally specified set of explanatory variables and powers of the predicted values (squared, cubic, and the fourth power) did not reveal statistical significance of omitted variable bias. Multicollinearity between the lambda and other explanatory variables, particularly the transplant type variable is not strong. The highest values of variance inflation factors were 3.85 for the year one model and 4.00 for the year three model.

Two baseline variables measured at pre-transplant: ability to work for pay and working status that were found different between the two groups, were not specified in the outcome equation. The variable capturing ability to work at the time of pre-transplant was measured long enough ago (i.e., about one and a half year) that it should not affect the utility outcome after transplant. A transplant intervention offers positive impacts on such factors after transplant. In conclusion, as statistically valid and controlling for potential differences at pre-transplant, we can accept the findings that at year 1 and year 3, SPK recipients have higher expected utilities than KTA recipients.

B. Utilities used in Markov model

Table 5.16 summarizes year one and year three utilities to be assigned to the reference case in the Markov model for each of the six health states. For the two health states: SPK with both pancreas and kidney grafts functioning and KTA with kidney graft functioning, utility weights to be assigned in each cycle of Markov simulation were derived from QWB scores that were predicted on the whole 12,593 observations of the reference population. Characteristics of the reference population that appear in the estimation model of Gross et al. study are age and gender.

Table 5.16 Utilities for health states assigned to the reference case analysis

Health states	Year 1 utility	Year 3 utility	How values are estimated
SPK both grafts functioning	0.71	0.75	The utilities are determined from Gross et al study. They are consistent with the utility for non-diabetic patients at post-transplantation (0.73) reported by Laupacis et al (1996). Wu et al (1998) reported the predicted QWB scores of patients with IDDM ranged from 0.70-0.76 based on the pre-existing diabetes complications. The present study assumed that SPK is performed for those who have multiple complications of diabetes. Although, SPK recipients are free from insulin therapy and restriction lifestyles, they still suffer from pre-existing diabetes complications which were not reversible e.g., blindness, and some side effects of immunosuppressive agents.
SPK pancreas graft failed	0.62	0.62	The utility is determined from Gross et al study. It is consistent with the utility value of 0.62 for patients with diabetes who have kidney graft functioning at post-transplantation reported by Laupacis et al (1996). The utility of 0.60 was used for this health state in a recent CEA of SPK (Douzdjian et al., 1998).
SPK kidney graft failed	0.58	0.58	The utility is based on Laupacis et al (1996) report of the utility of 0.58 for those without diabetes who are on dialysis. The predicted QWB scores unspecific to diabetes population were reported at 0.61 for hemodialysis patients and 0.62 for patients with peritoneal-dialysis (Fryback et al., 1995).
SPK both grafts failed	0.49	0.49	The utility is based on Laupacis et al's report (1996) for those with diabetes who were on dialysis. This value is chose as the middle ground between the utility used in CEAs in IDDM population. A CEA of SPK used the utility of 0.40 for this health state (Douzdjian et al., 1998), and a CEA of intensive insulin therapy conducted by DCCT trial used the utility of 0.61 for patient with IDDM and ESRD (DCCT, 1996). Thus sensitivity analysis is performed.
KTA kidney graft functioning	0.65	0.64	The utilities are derived from Gross et al study. The value at year 3 is consistent with the utility for patients with diabetes who has kidney graft functioning at post-transplantation reported by Laupacis et al. (1996).
KTA kidney graft failed	0.49	0.49	The values are based on Laupacis et al.'s report (1996) of the utility of 0.49 for those with diabetes who were on dialysis. This health state is equivalent to SPK recipients with both grafts failed, and they share the same rationale. A sensitivity analysis is performed.

For the year one data, a parsimonious model that contains transplant type, age, gender, and Karnofsky score yields regression coefficient of SPK dummy variable of 0.06, which is robust, as compared to the model in Table 5.16. Assuming the mean Karnofsky score of 70 for the reference population, the successful SPK health state has the mean predicted QWB of 0.712 whereas the successful KTA health state has QWB of 0.652 for year 1. For the year three data, the regression coefficient of the SPK group indicator in the model containing only age and gender as covariates is 0.11, which is similar to the model in Table 5.16. The predicted QWB for year three is 0.749 for successful SPK and 0.637 for successful KTA.

Based on Gross et al.'s study, eleven SPK recipients with failed pancreas graft who responded to the study questionnaire at year one had mean predicted QWB scores of 0.62 (S.D.=0.09). This value is assigned to the health state of SPK with pancreas graft failure.

In a CEA of kidney retransplant policy, Horberger et al. (1997) assigned the utilities of 0.65 to observations in the first 6 month after kidney graft failure and 0.68 thereafter. These utility weights were based on the standard gamble technique. These values are not much different from the mean score of 0.62 in those who had kidney graft loss that was based on a time trade-off measure as reported by Laupacis et al. (1996). However, these utilities are not specific to the kidney transplant recipients with type I diabetes. Only the work reported by Laupacis et al. (1996) focused on the subgroup of patients with diabetic ESRD. They reported that pre-transplant patients with diabetic ESRD had a mean score of 0.49 at pre-transplant, and 0.62 at 1 year post-transplant, whereas non-diabetic patients reported the utility of 0.58 at pre-transplant and 0.73 at one year after transplant.

Most CEAs relating to kidney transplantation use the utility of 0.84 for those who have graft functioning, and that of 0.60-0.65 for those who have graft failed, in the reference case analysis. It is possible that there exists an impact of diabetes on utility. Patients on dialysis and kidney transplant recipients with diabetes reported lower utilities measured by a time trade off measure than those without nondiabetes (Laupacis et al., 1996). The utilities assigned to the health states in the present study (Table 5.16) seems to provide relatively conservative estimates for patients with kidney transplant or on dialysis. This is because the utility of SPK with both graft functioning obtained from Gross et al.' study is less than the values assigned in prior CEA of SPK and the lowest utility estimates from published studies were chosen for other health states.

VI. Cost-Effectiveness in the Reference Case

An incorporation of morbidity and mortality consequences into a single measure of quality-adjusted life years (QALYs) was accomplished by using Markov simulation. The reference case for cost-effectiveness analysis in this study is based on the mean predicted values of the 12,593 Medicare ESRD population who had type I diabetes as a cause of renal failure and received a primary kidney transplant during 1988 to 1998. Table 5.17 summarizes cost-effectiveness of SPK as compared to KTA for the reference population. Based on the reference case analysis, SPK yields higher effectiveness in life expectancy (13.40 years vs. 10.55 years) and QALYs (9.16 vs. 6.43) than does KTA. Lifetime costs of treatment are $407,336 for SPK and $319,633 for KTA. When undiscounted costs are used, SPK would have an increased cost of $87,703 and would increase the cohort's life expectancy by an average 2.85 years. Using discounting rate at 3% for both costs and effectiveness, the incremental cost-effectiveness ratio for SPK compared to KTA is $33,996 per QALY gained.

Table 5.17 Cost effectiveness for the reference case based on mean characteristics of the reference population

	SPK	KTA
Life expectancy (years)	13.40	10.55
Lifetime cost (1998 U.S. dollars)		
Undiscounted	407,336.31	319,632.87
Discounted 3%	325,395.94	262,843.13
Discounted 5%	289,344.65	235,602.48
QALY		
Undiscounted	9.16	6.43
Discounted 3%	7.11	5.27
Discounted 5%	6.17	4.70
Additional cost per QALY gained (1998 U.S. dollars)		
Undiscounted	32,125.80/QALY	
Discounted 3%	33,996.09/QALY	
Discounted 5%	36,559.30/QALY	

Discounting assumes that money saved or spent and year saved or lost in the future are not worth as much as they are today. This process reduces future costs and future life years so that up-front costs, such as transplant surgery costs weigh more than the projected future costs of potential late complications from the disease. Because discounting particularly of survival benefits, is somewhat controversial, costs and life expectancy without discounting were calculated. The additional cost per life-year gained is $30,773. Results of the analysis unadjusted for health-related quality of life showed somewhat difference in the cost-effectiveness ratio.

VII. Sensitivity Analysis

The results suggest that SPK usually provides improved quality-adjusted life expectancy over KTA and that the cost of this advantage is not too high. Sensitivity of the incremental cost-effectiveness was examined by varying the following elements: (1) failure rate of pancreas graft for SPK health states, (2) cost ratio of pancreas-kidney to kidney organ acquisitions for both graft functioning SPK health state, (3) the intensive insulin therapy for KTA health states and pancreas graft failed SPK health states, and (3) utilities for general population of kidney transplant based on widely-cited literature. Key findings of the sensitivity analyses are shown in Table 5.18. For each change in an underlying assumption, Table 5.18 shows the difference between SPK and KTA in QALY and lifetime costs of direct medical care. The incremental cost-effectiveness ratios of SPK over KTA are shown in the last column.

In the reference case analysis, discounting both costs and effects at 3% per year was used. By increasing the discount rate to 5%, the incremental cost per quality-adjusted year of life gained is $36,559.

Sensitivity analyses show the reference case result is quite insensitive to variation in the failure rates of pancreas graft. Doubling the pancreas graft failure rate from 2% to 4% increases the cost per quality-adjusted year of life gained by 13% from $34,619 to $ 39,281.

Table 5.18 Results of sensitivity analysis

Variable	dQALY[a]	dCost[b]	dCost/dQALY ($/QALY gained)
Discount rate in the reference case			
0%	2.73	87,703.44	32,125.80
3%	1.84	62,552.81	33,996.09
5%	1.47	53,742.17	36,559.30
Pancreas graft failure rate[c]			
2%	1.78	61,620.93	34,618.50
3%	1.60	58,976.70	36,860.44
4%	1.44	56,564.53	39,280.92
Ratio of pancreas organ acquisition cost[c]			
1.2	1.84	57,573.40	31,289.89
2.0	1.84	69,053.30	37,528.97
Cost of intensive insulin therapy[c,d]	1.84	51,509.15	27,994.10
Utilities based on general kidney transplant population[e]			
Presence of effect of pancreas transplant	2.15	62,552.81	29,094.33
Absence of effect of pancreas transplant	1.27	62,552.81	49,254.18

[a] dQALY = QALY of SPK minus QALY of KTA

[b] dCost = Lifetime cost of SPK minus lifetime cost of KTA (in 1998 U.S. dollars)

[c] dCost/dQALY for all categories was discounted using a rate of 3%.

[d] The effect of intensive insulin therapy used in KTA and SPK with pancreas graft failure

[e] See Appendix

Estimates of cost-effectiveness ratio are not much influenced by cost of organ acquisition. The results, however, are quite sensitive to the use of intensive insulin therapy instead of conventional insulin therapy. The values of $3,500 per year for the annual costs of intensive insulin therapy were used (Wu et al., 1998). If the intensive insulin therapy was delivered by multiple daily injection, the lifetime cost of KTA would increase to $336,386. Implementing the multiple daily injection of insulin would result in a decrease in the incremental cost-effectiveness ratio for SPK to $27,994 per QALY.

Most previous CEA of kidney transplantation used the value of 0.84 for utility associated with the health state of KTA graft functioning and 0.68 for KTA graft failure with dialysis. However, these published utilities are not specific to the kidney transplant recipients who had type I diabetes as an underlying disease and as a cause of renal failure. First, the sensitivity analysis considers the values from the general kidney transplant recipients for KTA and adjusted for SPK by using the results from selectivity-corrected model in the present study. The selectivity-corrected estimation shows that pancreas transplant yield a higher utility of 0.067 to SPK than KTA at year 1 and 0.11 at year 3. Derivation of the utilities for all health states using these values is shown in Appendix. By using these values, the incremental cost-effectiveness ratio is $29,094 per QALY. SPK yields 8.66 QALYs and KTA yield 6.51 QALYs, when using a discounting rate of 3%. Second, in the worse case scenario with an absence of the beneficial effect of additional pancreas transplant, the sensitivity analysis is based on the values of the utility of 0.84 for kidney graft functioning and 0.68 for kidney graft failure (Torrance, 1987; Fryback, 1995; DCCT, 1996). The incremental cost-effectiveness ratio increases to $49,254 per QALY.

CHAPTER 6

DISCUSSION AND CONCLUSION

This concluding chapter consists of three major sections. The first section summarizes major findings from this study. Section two compares the findings from this study with previous studies that answered similar research questions, and also covers issues on the strengths and weakness of this CEA study. Furthermore, issues for future research are also discussed. Section three discusses implications of the findings from this study to public policy.

I. Summary of Major Findings

This study answered two major questions specific to transplant options provided for persons with type I diabetes and end-stage renal disease. The first question is, "what are the lifetime benefits and costs of SPK as compared to KTA with continued insulin therapy?" The second question is, "would more costly SPK be preferable to KTA with continued insulin therapy under the perspective of the health care sector?" This study found that the lifetime benefits of SPK markedly exceed the lifetime benefits of KTA. The reference case is the Medicare ESRD population who have type I diabetes as a cause of renal failure and received primary cadaveric kidney transplant as SPK or KTA. In the reference case analysis, SPK prolongs both unadjusted and quality-adjusted life expectancies and incurs higher lifetime costs per patient as compared to KTA. Estimated life expectancy is 13.4 years for an SPK recipient and 10.6 years for a KTA recipient. When life expectancy is adjusted by quality of life, SPK generates 9.16 QALYs and KTA generates 6.43 QALYs.

As compared to KTA, SPK is associated with a 2.9-year increase in survival and a 2.7-year increase in quality-of-life adjusted life expectancy. The incremental cost-effectiveness ratios are $30,773 per year of life gained and $33,996 per additional QALY (discounted at 3%) for SPK. In general, these sums represent a good monetary value for investment. They are in the range usually considered to be cost-effective and are similar to the cost-effectiveness ratios for other medical treatments that have been widely adopted in the US. Based on sensitivity analyses, the incremental cost-effectiveness ratios of SPK are robust over a wide range of variable estimates.

The divergence between SPK and KTA in patient and kidney graft survivals was found after 4 years following transplantation. Among the transplant recipients who survived with kidney graft function through 4 years after the transplantation, SPK reduces the risk of death by 42% and the risk due to kidney graft failure by 36% as compared to KTA. These results are consistent with previous studies by Becker et al. (1999), Smetes et al. (1999), and Tyden et al. (1999). This implies that SPK can offer improvement in long-term pathophysiological mechanisms related to diabetes complications.

An improvement in SPK transplant surgery techniques is evident as the length of hospital stay decreased from 22 days in 1991 to 15 days in 1998. The hospitalization costs related to SPK transplant surgery, excluding organ acquisition costs and professional fees, dramatically decreased from $64,597 in 1991 to $55,458 in 1998. The costs of KTA have decreased over time as well, and the hospital stay was shortened from 14 days in 1991 to 9.5 days in 1998.

First-year costs following transplant surgery for SPK are much higher than those of KTA. Among those with graft function, the follow-up costs of SPK remain higher than KTA at year two. The annual costs after the second year following transplantation for SPK (years 3 to 8) and KTA (years 3 to 9) are relatively stable over time. The average annual cost after year two for SPK ($16,718) is slightly lower than KTA ($17,052). All costs reported here exclude insulin therapy and out-of-pocket prescription drugs.

This study also found that for those who had successful graft functioning, SPK yields higher utilities at year one and year three after transplantation than KTA does. The mean value of predicted QWB scores for SPK is 0.71 and that for KTA is 0.65 at year one, on a scale where 0 equals death and 1 equals perfect health. At year three, the mean values are 0.75 and 0.64 for SPK and KTA, respectively. The difference in the predicted QWB mean score between SPK and KTA is widened from 0.067 in year one to 0.11 in year three. This finding is consistent with the fact that surgical complications and readmissions rate at year one for SPK are higher than KTA (Holohan, 1995; Troopman et al., 1998).

The results from this study provide explicit information based on the health care sector perspective about the incremental benefits and costs of choosing one transplant procedure over another for type I diabetic ESRD patients. SPK rather than KTA should be offered to this population.

II. Discussion of Related Studies and Study Limitations

The inclusion criteria in this study were recipients of the primary cadaveric kidney transplant who had type I diabetes as a cause of renal failure. This represents a substantial population of patients, therefore, it may not jeopardize generalizability of the study results. For the patients receiving cadaveric donor kidneys, the fraction of repeat-transplant candidates has been declining steadily from about 15% in 1990 to 12% in 1993 as the kidney transplant technology has been substantially improving (USRDS, 1995). Currently, the percentage of kidney retransplantation remains about 12%. Living-related kidney donors account for 30% of all kidney transplantation performed each year. Subsequent cadaveric pancreas transplant after receiving kidney transplant (i.e., PAK) has been performed in 15% of patients with type I diabetes and renal failure.

This study takes the health care sector perspective for cost-effectiveness analysis. Medicare payments were not converted to economic costs. To obtain opportunity costs, department-level cost-to-charge ratios need to be applied to the charge amounts from the MedPAR files. Also, the costs need to be adjusted for geographic variation using the area wage index Medicare applies in calibrating its payments to institutional providers of care (Lipscomb et al., 1998). This would be the case if the study took the societal perspective as the Panel recommended using the opportunity costs for the numerator of cost-effectiveness ratio.

The findings of the present study are in the range reported by several prior studies. Patient and graft survivals reported in this CEA are consistent with those in other reports (IPTR, 1999; USRDS, 1999b). Prior analyses reported life expectancy of 15.33 years, QALY of 6.94 and lifetime cost of $275,497 for a person receiving first-kidney transplant (Horberger, 1997). However, these figures were estimated from patients with renal failure from any causes. Wu et al. (1998) obtained predicted QWB scores from persons with type I diabetes and complications; with an average age of 60.6 years, the predicted QWB score was 0.663 (0.5-0.82). An extended study of the DCCT on CEA showed that when comparing intensive insulin therapy with conventional insulin therapy for the management of insulin-dependent diabetes mellitus, the incremental cost per QALY was $28,661 at a discount rate of 3% (DCCT, 1996).

There have been a few reports that applied decision-analytical techniques to SPK. Each of these studies used simple decision tree models with a timeframe less than 5 years, and the branch probabilities relied on published survival interpolated from early years of SPK transplant. In such reports, survivals cannot be distinguished between those who died with graft function and those with graft failure. These figures are required if a valid life expectancy is calculated. The present study used a primary data source: the national transplant registry to derive the transitional probabilities specific to various health states with respect to graft status. This strategy gives the most complete picture of how different treatment groups fared over time with respect to patient survival and graft status. The Markov model technique is superior to a decision tree model in that it allows investigators to calculate life expectancy, lifetime benefits, and lifetime costs (Naimark et al., 1999; Sorbenger et al., 1993). In addition, in this study the individual claim-level data on costs was used to obtain the cost estimates and utility estimates for graft functioning health states which came from the primary data source of a longitudinal QOL study (Gross et al., in press).

It may be argued that the best available patient and kidney graft survival data were used in this study. The ESRD Program Management and Medical Information System (PMMIS) maintained by HCFA updates the death status and kidney graft status regularly (HCFA report, 1996). Furthermore, the date of death was obtained from the

Master Beneficiary Records that are maintained for all Medicare beneficiaries or the ESRD Death Notification Form (HCFA-2746). Lastly, the date of transplant was obtained from the transplant files provided to HCFA from the Organ Procurement and Transplant Network (OPTN) or from the inpatient hospital bill (HCFA-UB-92). The date of transplant failure was either obtained from the OPTN, calculated based on a record of outpatient dialysis sessions, or based on the date of a subsequent transplant.

For the pancreas graft failure rate, the follow up of graft status and its verification process may not be as complete as other endpoints. This study used a sensitivity analysis by varying the pancreas graft failure rates to deal with this uncertainty.

One major limitation in this study is that variable estimates assigned to the Markov model were obtained from databases in which patients were not randomly assigned to the transplant choice. Rather than relying on the observed values, this study used statistical models to predict the outcomes for the reference population by controlling for the underlying difference between SPK and KTA as much as possible. Specifically, patient death rates, graft failure rates, and annual cost estimates were adjusted for the available demographic characteristics: age, gender, and race. An estimation of utility weights for the graft functioning health states of SPK and KTA was based on selectivity-corrected models.

This study derived information on patient and graft survivals, quality of life, and costs from the patient-level observations over a relatively longer follow-up period as compared to previous works. However, an estimation of the lifetime benefits and costs from the Markov simulation model required an imputation for missing data when the observed values were not available. The assumptions made in this study are conservative.

For example, this study assumed a constant probability for both SPK and KTA in both patient death rates and graft failure rates while the data from the available years seem to show that there is an increasing trend for KTA as compared to SPK. These may have underestimated the additional benefit of SPK on life expectancy.

This study derived cost data from Medicare which usually does not cover prescription drugs and their coverage for immunosuppressive drugs is limited to three years following kidney transplantation. Therefore, costs related to the required medications in maintenance therapy need to be addressed. Three major drug classes commonly used by the target population in this study are insulin, drugs used in the treatments of diabetes complications, and immunosuppressive agents. Cost of insulin therapy was added into the KTA health states and SPK health states that have pancreas graft failure. Drugs used in diabetes complication treatments were not accounted for in this study, because the study assumes treatment costs for diabetes complications are similar between SPK and KTA. This assumption may have underestimated the benefits of pancreas transplant and, consequently, underestimated the incremental cost-effectiveness ratio of SPK.

Immunosuppressive regimens used for SPK recipients are not substantively different than KTA recipients receiving cadaveric organ transplant (Sutherland, 1997), but the actual dosage regimens of immunosuppressive therapy vary from center to center. Generally, for both SPK and KTA recipients, cyclosporin in combination with azathioprine (AZA), or prednisolone, or both has been the dominant regimen. In the mid 1990s, FK-506 (tacolimus) has replaced cyclosporin for some patients and increasingly mycrophenolate mofetil (MMF) is used to replace azathioprine. Sirolimus is a newer alternative to MMF or AZA. The introduction of FK-506 and MMF, alternatives to cyclosporin and AZA, are associated with improved patient survivals and better graft survivals (Jordan et al., 1998; IPTR, 1999).

In July 1995, Medicare began to cover immunosuppressive therapy for the period of three years following the hospital discharge of transplant surgery. Certain observations in this study obtained from Medicare Part B claim records may or may not contain cost data on such therapy. This study did not account specifically for the costs of immunosuppressive therapy. The estimated lifetime costs may be diluted, especially for SPK and KTA recipients who had transplantation before 1995. However, the results on incremental cost-effectiveness ratios are not biased because the change in the Medicare coverage policy was implemented at the same time, has the same effect on both SPK and KTA, and the pattern of immunosuppressive therapy between SPK and KTA is similar.

Under the health care sector perspective, this study included neither the patient time costs nor the indirect costs associated with productivity loss due to disability and premature mortality. To the extent that SPK requires patient time associated with readmission due to pancreas transplant complications in the first couple of years more than KTA, the study would have underestimated the incremental cost of SPK. In contrast, KTA recipients require more time in daily management of diabetes. The inclusion of patient time costs would be the case if the study takes the societal perspective.

An inclusion of the indirect costs or potential productivity losses in an economic evaluation used to be controversial. Russel (1996) stated that "*estimates of earnings help to describe the consequences of better health in greater health in greater detail, but they are not an addition to the health effects. To include them as a separate item is to count* *some of the effects twice, once as a gain in health and again as a savings to be subtracted from program costs*". The CEA in this study obtained the utility weights from the predicted Quality of Well Being (QWB) scores that were transformed from SF-36 health profiles and from the time-trade off measure that was from the published literature. The QWB scale is a generic preference-weighted health state classification system that can capture the effects of morbidity on productivity and leisure and has been used for an evaluation of several medical and surgical procedures. QWB has been claimed as the most widely used measure for overall health that can be used for the calculation of QALYs (Gold et al., 1996).

An application of regression to derive predicted QWB scores from SF-36 data raises a concern because the equation was based on general population with the mean age of 64.1 years and was not disease-specific data. Since type I diabetic patients generally report values on the SF-36 lower than the general population does, the equation used in this study may not be appropriate (Fryback, 1995). However, when averaged, the QWB scores used in the present study are consistent with those from previous studies of a type I diabetes population and patients from a renal dialysis clinic (Fryback et al., 1993; Fryback et al., 1997; Wu et al., 1998). Fryback et al. (1998) conducted a cross validation in a subgroup of patients from a renal dialysis clinic. The mean predicted from SF-36 data and observed QWB scores were 0.655 and 0.653 for patients with non-end-stage renal insufficiency (N=16), 0.606 and 0.593 for hemodialysis patients (N=22), and 0.624 and 0.602 for peritoneal dialysis patients (N=19) respectively.

The finding that SPK provides an advantage over KTA is not surprising, but the sensitivity of the decision to assign the utility, based on widely cited literature that is unspecific to diabetes population, shows that determination of the utility should be an important goal for future research. Under the worse case scenario that the additional pancreas transplant would not have improved quality of life, the incremental cost-effectiveness ratio of SPK would increase by 45% to $49,254 per QALY.

It has been widely accepted that utility is a hard concept and its measurement is controversial. In addition, the theory and empirical evidence regarding the relationship between individual and market rates of time preference are unsettled. In the present study, results including cost per life year saved and undiscounted incremental cost-effectiveness ratio of the reference case analysis are reported in addition to the recommended measure and incremental costs per QALY gained at a discount rate of 3%. Many other issues apart from cost-effectiveness, such as ethical and political considerations, affect the implementation of a new technology. However, they are not taken into account in the present study. The issue has been raised that transplantation has been criticized as too costly compared with other health care needs, but this is beyond the scope of this study.

III. Implications to Health Care Financing Policy

In conclusion, the model of the present CEA can provide reliable estimates of life expectancy, lifetime benefits, and lifetime costs. Therefore, it provides health policy makers a useful tool to justify financing SPK for type I diabetic ESRD patients.

The gain in life expectancy is an important outcome for a treatment of chronic illness. It can help patients and physicians decide if the benefits of a medical procedure outweigh its harm. Information on costs incurred by such a procedure for an additional benefit can help the third-party payers in deciding which procedures should be covered.

A comparison of cost-effectiveness ratios between medical procedures in terms of costs per QALY gained has become popular. The motivation behind this approach is to place the findings in a broader context. Furthermore, the comparison across studies is important in assessment of the value of different procedures in disparate medical fields. When the commonly suggested guideline of $50,000 per QALY gained is used as the definition of a cost-effective intervention (Laupacis et al., 1992), SPK can be considered a cost-effective intervention ($33,996 per additional QALY based on 3% discount rate). In addition, its cost-effectiveness ratio is comparable to other well-accepted interventions as shown in the summary table below. The results collected here are from other studies that used similar approaches to the present studies in which measures for utility capture indirect effects and patient time costs are not included in the analyses.

Incremental cost-utility ratio for selected health care programs

Program	$ per QALY*	Reference
Treating type II diabetes with the goal of normoglycemia	18,358	Eastman et al., 1997
Coronary artery bypass graft, without prior congestive heart disease	28,547	Graham et al., 1998
Bone marrow transplant, second relapse of Hodgkin disease	28,767	Smith et al., 1993
Intensive insulin therapy for type I diabetes	32,885	DCCT, 1996
Interferon-α for chronic myelogenous leukemia	38,209	Kattan et al., 1996
Calcium channel blocker, diastolic blood pressure > 95 mmHg	47,212	Graham et al., 1998
Heart transplantation	104,000	Sacchi et al., 1995
Annual screening for diabetic retinopathy	107,510	Vijan et al., 2000
Lung transplantation	202,879	Ramsey et al., 1995

* in 1998 U.S. dollars

Compared with other medical procedures, the advantage gained by SPK over KTA seems to be comparable to other well-accepted interventions. The CEA framework of this study follows the guidelines recommended by a national committee. The cost-effectiveness ratio results can be compared with other health care interventions for prioritizing resource allocation.

Of all the kidney transplant recipients who were covered by the Medicare ESRD program, about 30% report diabetes as their primary diagnosis, and 80% of them have type I diabetes. During 1994–1998, there were about 1,000 type I diabetic patients per year who received primary cadaveric KTA and met the eligibility criteria for this study. If the gain of 2.7 years in quality-of-life adjusted survivals from SPK is extrapolated to these KTA recipients, SPK will result in approximately 2,700 additional quality-adjusted life years. Taken into account of the discounting rate of 3%, if the additional cost over lifetime of $62,553 per patient for SPK is applied to this population, SPK will cost approximately $62.5 million more than KTA over the lifetime of this population. If the additional benefits of SPK, measured in terms of QALY, are compared with the incremental costs of SPK and both benefits and costs are discounted at 3% per year, then SPK will cost approximately $34 million for 1000 QALYs of these 1,000 patients.

The results of this simulation model, under a variety of scenarios, the cost-effectiveness for SPK is well within the range of cost-effectiveness ratios considered to represent a good value.

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APPENDIX

Values of utilities in the sensitivity analysis

Presence of effect of pancreas transplant

Utilities based on general kidney transplant population and accounted for the effect of pancreas transplant that yields a higher utility of 0.067 to SPK than KTA at year 1 and 0.11 at year 3.

Heath State	SPK both grafts functioning	SPK kidney graft failure	SPK pancreas graft failure	SPK both grafts failure	KTA kidney graft functioning	KTA kidney graft failure
year 1	0.874	0.714	0.806	0.646	0.806	0.646
year 3	0.895	0.735	0.785	0.625	0.785	0.625

Absence of effect of pancreas transplant

The values of the utility are 0.84 for kidney graft functioning and 0.68 for kidney graft failure, with the absence of effects of pancreas transplant.

Heath State	SPK both grafts functioning	SPK kidney graft failure	SPK pancreas graft failure	SPK both grafts failure	KTA kidney graft functioning	KTA kidney graft failure
year 1	0.84	0.68	0.84	0.68	0.84	0.68
year 3	0.84	0.68	0.84	0.68	0.84	0.68

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